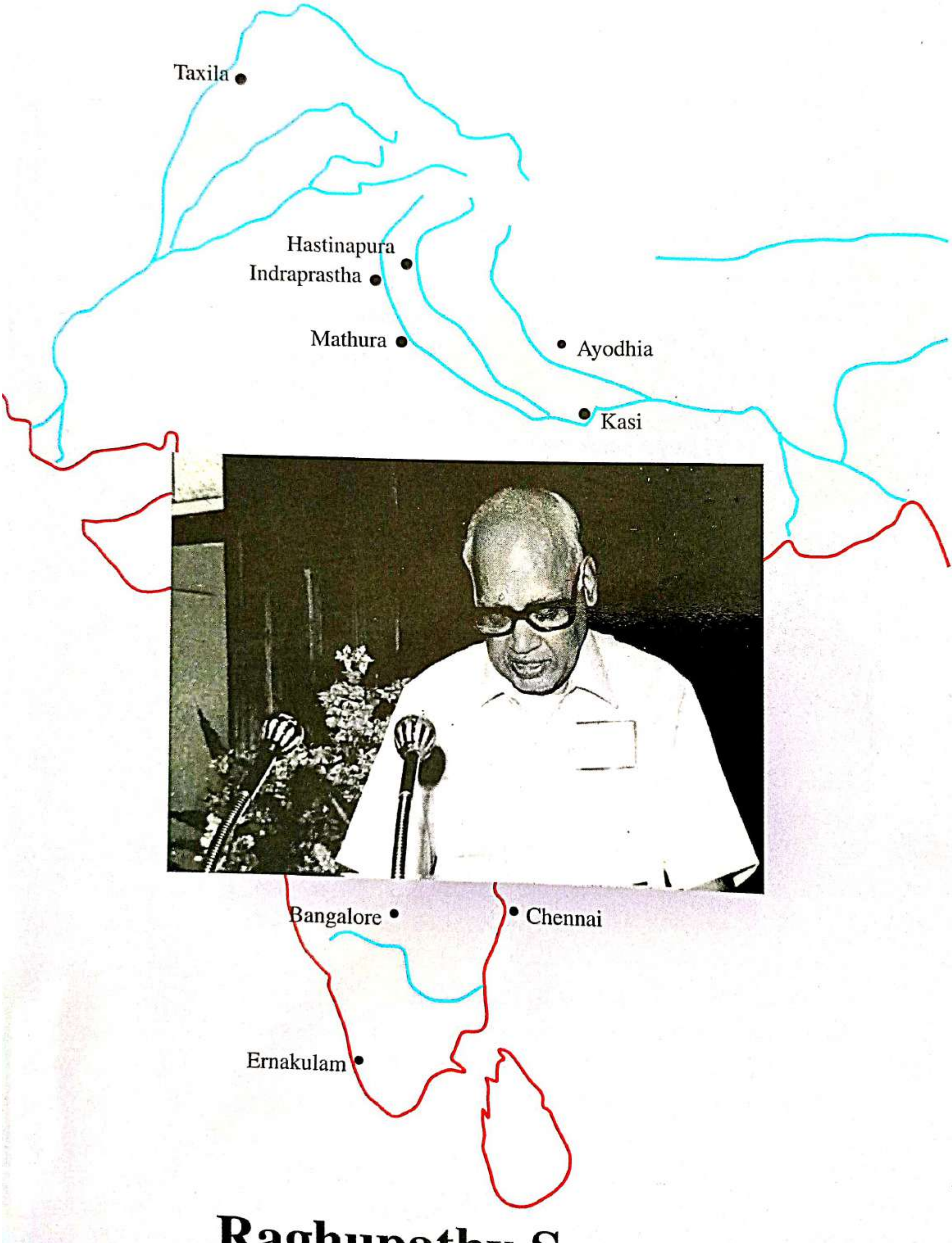
RAMACHANDRAN



Raghupathy Sarma

RAMACHANDRAN

A Biography of the Famous Indian Biophysicist

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A Note from the Publisher

Adenine is delighted and proud to publish RAMACHANDRAN because we believe that the volume will provide new energy and incentive to the gifted students in the current young generation in India to follow the path of Ramachandran. We deliberately chose an ancient map of India for the background. The intellectual intensity and straightforwardness of Ramachandran reminded us of the ancient learning center Taxila, founded by Bharata, where the great Indian epic *Mahabharatha* was first recited. GNR reminded us of the form and frame of Yudhishthira. Indraprastha where Yudhishthira ruled over and conducted Rajasuya is definitely the Madras and the Glory Days (p. 39). Sir A. L. Mudaliar, to us, is an avaratha of Krishna and looked after Ramachandran. Hastinapura represents Bangalore and the Bad Days (p. 125); thank God there were several Viduras in this Hastinapura to comfort GNR from the Duryodhana crowd. Finally there is this reincarnation of Krishna in the form of C. N. R. Rao who literally pulled GNR out and rescued him. But, by this time, GNR absorbed so much assault and damage that his physical and emotional health could not keep up. What a sad story. India lost what would have become the most powerful center in structural biology in the world. India lost the Indraprastha in structural biology.

On page 134 there is a remarkable interview between C. N. R. Rao and the author. Take home lesson: Love, respect, understanding, cooperation and tolerance among colleagues will tranform an institution into greatness.

RAMACHANDRAN

A Biography of
Gopalasamudram Narayana Ramachandran,
The Famous Indian Biophysicist

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Cover Illustration: G. N. Ramachandran thanking the gathering at his 60th birthday celebration, Madras University, Chennai, India, January 1982. The background map shows some of the ancient cities in India from her illustrious civilization.

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Preface

Gopalasamudram Narayana Ramachandran, GNR to those who know him well, is one of the most brilliant Indian scientists of this century. He has been rightly called "the father of molecular biophysics in India." He was a pioneer in that field even when the subject was just starting to take shape in the advanced countries of the Western world. He made several very important discoveries in molecular biophysics, especially in the study of protein structures, at a time when very little was known about them. Ramachandran's formulation of the rules for describing conformations of polypeptides, polysaccharides, and polynucleotides was responsible for initiating a new field of study on conformations of macromolecules. His permanent imprint in this field, the "Ramachandran phi-psi plot" or simply the "Ramachandran diagram", has become a standard description of protein structures in every modern publication.

Ramachandran also discovered the triple–helical structure of the connective tissue protein called collagen, one of the more abundant mammalian proteins in the world. Remarkably, the structure of collagen he proposed over four decades ago has survived the scrutiny of numerous experiments. Ramachandran has also been an innovator in several other important areas of molecular biophysics, including X-ray crystallography, and three– dimensional image reconstructions of electron microscopic images. He started the departments of Molecular Biophysics at the University of Madras and later at the Indian Institute of Science in Bangalore. These two departments have become leading centers for research in biophysics and the education of graduate students in India.

Ramachandran began his scientific career as a student of Sir C. V. Raman, the first Indian Nobel laureate in physics. He conducted a brief period of study in Cambridge, England, in the laboratory of yet another Nobel laureate, Sir William Lawrence Bragg. On his return to India, Ramachandran was appointed as an assistant professor in the Department of Physics at the Indian Institute of Science. There he started research in X-ray crystallography, a tradition that continues to this day. After a few years he moved to the University of Madras where he became one of the youngest professors in the newly created Department of Physics. There he built one of the finest programs devoted to molecular biophysics. Several years later he returned to the Indian Institute of Science and again started a Department of Molecular Biophysics that is one of the best departments in that field in India with an international reputation.

Ramachandran has never retired from intellectual activity as he constantly explores various fields like Indian philosophy, artificial intelligence, etc. His favorite topic is what is called Syaad Nyaaya, "the doctrine of may be," an age-old system in Jain philosophy. According to this system, any logical statement has more than two truth-values: it may be true, it may be false, or it may be doubtful. In a remarkable series of papers he interpreted the philosophical ideas of Syaad Nyaaya in a mathematical form which he called "Boolean vector matrix formulation." In his opinion the ideas expressed in these papers have potential applications in the field of artificial intelligence.

Most of Ramachandran's major scientific contributions were made against endless odds, at a time when scientific research and creativity had a low priority in India. The country had just achieved its independence from British rule and was trying to solve more immediate problems associated with building a new nation and improving the living standards of its enormous population. Despite such conditions, Ramachandran was able to inspire a large number of young people, first in Madras and later in Bangalore, to take up careers in science. Many of these students, including myself, have gone on to successful careers in science and made significant contributions in various aspects of biophysics throughout the world.

In addition to being a highly creative scientist, Ramachandran is a man of very high integrity and moral principles, as well as a generous person. He has a deep interest in philosophy and in classical Indian and Western music. He is a truly patriotic Indian with an abiding love for his country. He had numerous and lucrative opportunities to pursue his research career in many leading universities in the Western world, but he decided to stay in India, fight the bureaucracy, carry out his research interests, and inspire many young Indian students.

This book is about the life and science of Ramachandran, a remarkably creative individual with an active mind that never relaxed, constantly striving to shed light on one problem or another. His life has been one of varied experiences punctuated by ups and downs, success and failure, as is the case with many other famous scientists of our times. Ramachandran suffered serious psychiatric problems during most of his adult life. Fortunately they did not impact on his scientific creativity or productivity; it simply added a new dimension to his life. In spite of all that he put India on the map of molecular biophysics. Clearly, Ramachandran belongs in the same league as some of the most famous Indian scientists of this century, for example Sir C. V. Raman, M. N. Saha, or S. N. Bose (of Bose-Einstein statistics fame). Clearly his contributions in the field of biophysics are of the Nobel Prize caliber.

Words cannot adequately express my gratitude to Professor and Mrs. Ramachandran for their enthusiastic blessing and cooperation in this project. Both of them graciously allowed me into their lives and constantly helped me and encouraged me throughout this work. I could never have written this without their active cooperation. In addition I have interviewed hundreds of people in preparing this story. It is impossible to list all their names, but I am very grateful to each of them.

I wish to thank the Department of Biochemistry and the State University of New York at Stony Brook for granting me sabbatical leave, which enabled me to collect most of the data used in preparing this document. I also wish to thank Professor C. N. R. Rao, President of the Jawaharlal Nehru Center for Advanced Scientific Research in Bangalore, for giving me a Fellowship to work on this project. I am also very grateful to Professor M. Vijayan and all the members of the Molecular Biophysics Unit in the Indian Institute of Science for accommodating me during my stay in Bangalore. I am also grateful to Professors Yathindra and Sundaram of the Biophysics Department at the Madras University for giving me access to some of the original files of Professor Ramachandran. Several friends offered invaluable suggestions during the writing of this book. Some of them read through the manuscript and made changes and useful comments. I am particularly grateful to Professor R. Chandrasekhar of Purdue University; Dr. S. Thyagaraja Rao of Ohio State University in Columbus, Ohio; Dr. A. Jayaraman, Emeritus Scientist from Bell Labs in New Jersey; Professor A. K. Ramadas of Purdue University; Dr. Radhakrishna Bhat of

Brookhaven National Laboratory in Long Island; Professor C. V. Krishnan of SUNY Stony Brook, and Professor Narayan Hegde of SUNY, Westbury campus. It is a pleasure to acknowledge the constant encouragement and frank discussions I had with Professor Ramachandran's children, Ramesh Narayan, Vijaya Ramachandran and Harishankar Ramachandran.

Last but not least, I could not have even attempted this project without the encouragement and help of my wife, Kasthuri, and my children, Naveen and Deepak. Kasthuri accompanied me on my sabbatical leave, where she graciously helped me sort out all the interviews and made my life in India pleasant.

1. Education

Gopalasamudram Narayana Ramachandran was born in 1922. His parents came from a typical South Indian Brahmin family in Ernakulam, near Cochin, a coastal city in the southern state of Kerala in India. At that time Cochin was ruled by a Maharajah and enjoyed considerable prosperity in comparison to other parts of colonial British India. The rulers of such states had full autonomy under the British and most Indian rulers maintained cordial relations with their colonial counterparts. The Maharajah of Cochin was an enlightened ruler, under whose aegis educational and cultural institutions thrived. For higher education Cochin had a college known as the Maharajah's College.

Ramachandran is the eldest son of G. R. Narayana Iyer and Lakshmi Ammal. Iyer was a well-known professor of mathematics at the Maharajah's College. He belonged to the pioneering generation of Brahmins who had diverged from their traditional role as priests and gone on to college to study english, physics, and chemistry. Eventually, he retired as the principal of Maharajah's College, a position similar to that of president at a college in the West.

In describing his father, Ramachandran says: "My father was an M.A. [Master of Arts] in mathematics and he was teaching in Tirunelveli, a small town in the present state of Tamil Nadu. He applied for a job in the Maharajah's College in Ernakulam, and was told that he should have an L.T. [Licentiate in Teaching] degree to qualify him for the position of a lecturer. Thereupon he went to Trivandrum [the capital of the State of Travancore, currently called Kerala] and earned himself an L.T. degree that enabled him to join the faculty of the mathematics department in Maharajah's College.

Because of his ability and thoroughness he became the most senior and respected member of the department and retired as the principal. He had a very sharp mind in mathematics and he used to teach me mathematics. I had been exposed to most of the theorems in analytical geometry even before I went to college. When I was in high school, he would bring books on mathematics from the library and give me some challenging theorems to prove every day. He would write equations and ask me to solve them. He was a wizard in mathematics."

Ramachandran was attracted to mathematics from the very beginning of his student life and flourished under the tutelage of his father. It was, and has continued to be, his favorite subject, giving him an advantage over his contemporaries in school and college, particularly when it came to mathematics courses and related subjects.

Ramachandran had his early schooling in a government-run school in Ernakulam. In those days the state-run schools maintained a very high standard of teaching, because the Maharajah of Cochin insisted upon hiring only the best teachers. Consequently, private schools had lower standards of education. Merit was the prime consideration for admission to the government schools, contrary to the situation that prevails now. Cochin was one of the most highly literate regions of India, with a literacy rate of about 60 percent even in the 1930s when the average in other parts of India was only between 5 and 10 percent. That high literacy level is maintained throughout the state of Kerala even now and the Ernakulam district recently declared 100 percent literacy. This achievement is a result of voluntary participation in the education provided by some of the more educated citizens of the district.

The British regime did not interfere too much in the administration of primary education, particularly in states ruled by Maharajahs or princes. Their only influence on the rulers and their states was through the British–appointed Diwaans, who were their chief representatives. The colonial rulers were happy as long as there was "peace" in the region. The British also never questioned the religious freedom of their subjects. In fact they always preferred orthodox Hindu Maharajahs who could be depended upon to maintain law and order in their states.

Dr. T. Ramakrishnan was one of Ramachandran's earliest colleagues. Now retired as professor and chairman of the Department of Microbiology in the Indian Institute of Science, he fondly recalls his association with Ramachandran. They had their schooling together and their careers took parallel tracks. He describes his association with the Ramachandran family as a story of three generations. Ramachandran's father, Professor Narayana Iyer and Ramakrishnan's father, Professor Karunakaran Nair, were colleagues in Maharajah's College in Ernakulam. Ramachandran's father taught mathematics, while Ramakrishnan's father taught zoology. Ramachandran and Ramakrishnan attended the same high school in Ernakulam and were in the same class until at least 1935. Their careers crossed once again at the Indian Institute of Science in the early 1970s. Ramachandran chaired the Molecular Biophysics Unit and Ramakrishnan was chairman of the Department of Microbiology. Ramachandran's youngest son, Hari, and Ramakrishnan's oldest son, Ramesh, were in the same class at school in Bangalore.

Professor Ramakrishnan recalls that in high school Ramachandran was an outstanding student, particularly in mathematics, always getting a perfect score of 100 percent on all his mathematics examinations. Even though the high school was located in Ernakulam, the educational curriculum of all area schools was administered from Madras, the largest city in South India. The region of control was known as the "Madras Presidency", and all high schools in it had to administer a centrally formulated examination for students at the end of their eleven years of schooling. This final examination was called the Secondary School Leaving Certificate (S.S.L.C.) examination. Neither the teachers nor the students had any knowledge as to who prepared the questions for the final examination, nor did students know which teachers actually graded their answers. Mathematics was the only subject in which students were able to score a perfect 100, in all other subjects, such as english, history, biology or other science subjects, students had to settle for a maximum of 60 to 70 percent.

After eleven years of high school, students spent two years in a college before starting their education for a first degree in science or humanities. This "intermediate course," or the First Arts (F.A.) or First Science (F.Sc.) program, did not lead to any specific degree. The students could choose to study one of many different subjects during these two years of college. Most students who wanted to continue their education in engineering or obtain a degree in mathematics, physics, or chemistry studied what was called MPC (mathematics, physics, and chemistry). Any student who wished to go to medical school or specialize in biology studied BPC (biology, physics, and chemistry). Everyone else studied what was called "arts" which consisted of history, social studies, or commerce. MPC was considered to be the most challenging and only the very best students ventured to take on those subjects.

Every student studied English in college. In addition, they had to learn two more languages: a regional language and a third language. In most cases this third language was Sanskrit. After the British left the country and India achieved independence, the third language of study included Hindi, the official language of India. The regional language in Ernakulam was Malayalam; therefore, Ramachandran studied Sanskrit and Malayalam during his years in school and college.

After completing the intermediate course and ranking first among several thousand students in the entire Madras state, Ramachandran decided to study physics for a B.Sc. (Honors) degree. This was a unique degree, quite different from a bachelor's degree with honors granted by some universities in North India. The B.Sc. (Honors) program in which Ramachandran enrolled consisted of an intense three–year specialization in any one subject chosen from physics, chemistry, mathematics, history, literature, or economics. Students in the honors class studied very little of any languages. However, a student in physics honors, for example, studied two years of mathematics as an auxiliary subject in addition to physics, while chemistry honors students studied two years of physics in addition to chemistry.

There was another interesting twist to the honors program. After three years of study, students had one chance to take and pass a set of cumulative final examinations in all of the relevant subjects. If for some reason a student failed in one or more subjects, the university recommended that the student be awarded the normal B.Sc. degree, a degree normally given after two years of study. This placed an enormous burden on the students to perform well in their final cumulative examinations. Completion of the B.Sc. (Honors) degree was considered to be equivalent to a master's degree in science, which in fact was granted by default after two years of passing the B.Sc (Honors).

Ramachandran, with his extensive interest and knowledge, could have easily studied for the honors degree in mathematics. But his father, himself a professor of mathematics, discouraged his son from joining the honors program in mathematics. He rightly felt that Ramachandran already knew so much mathematics that if he did join the honors program, his college teachers would have "nothing new" to teach him. Therefore, he advised Ramachandran to join physics honors and ask for special permission to study chemistry in place of mathematics as the subsidiary subject. Ramachandran always felt that this was a very wise choice on his part, as this introduction to chemistry helped him substantially in his later research.

The criteria for admission to the honors program were demanding. Only the very best students from the intermediate class were admitted. As a result, the enrollment in the B.Sc. (Honors) class was much smaller than in the B.Sc. class, and consisted of no more than a dozen students.

There were only three colleges in the Madras Presidency that offered the specialized honors programs in the science subjects: Presidency College in Madras, Madras Christian College in Thaambaram, and St. Joseph's College in Thiruchirapalli or Trichy, about 200 miles southwest of Madras.

All the colleges in the Madras Presidency were affiliated with the University of Madras, which controlled the curriculum for the various honors programs. The University of Madras, started by the British in 1857, was one of three oldest such universities in India, the others being the Universities of Bombay and Calcutta.

In 1939, Ramachandran was only 17 years old. For the first time in his life he left Ernakulam, the home of his parents and went to live in Trichy for three years to study physics and chemistry. St. Joseph's College was one of several institutions started by the Christian missionaries and had a reputation for offering a high–quality education combined with strict discipline. The Department of Physics in particular had some very well–known professors, two of whom seem to have stimulated Ramachandran's interest in physics, Professor P. E. Subramaniam, and a Jesuit priest by the name of Father Rajam. Both were supposed to be excellent teachers, the latter had written a textbook on modern physics, used by all students who studied the subject. "Modern" physics at that time included the study of atomic structure, the Bohr and Sommerfeld atomic models, and the theory of Relativity.

Ramachandran was a diligent student who almost never missed a lecture or laboratory work in his three years in college. The only exception was during the crucial three–week period before the notorious cumulative final examination for the B.Sc. (Honors) degree. Ramachandran was sick with jaundice and had to miss all the classes, while he recovered at his parents' home in Ernakulam. Yet in spite of his illness, Ramachandran again secured the first rank among all the physics honors students in the entire Madras Presidency.

Ranking first in the Madras University system among a set of very bright students in an honors class was an extraordinary achievement. As mentioned before, Presidency College in Madras was one of three colleges that offered the physics honors program, and it had a unique distinction of producing an abundant share of "firsts" in the university. The Presidential graduates became top class scientists and administrators in later life. Madras was after all the capital and attracted some of the very best students in South India.

A dozen years before Ramachandran's time, another bright young man by the name of S. Chandrasekhar secured the first rank in physics honors from Presidency College. He became a famous professor of astrophysics at the University of Chicago and was awarded the Nobel Prize in Physics in 1983 for his prediction fifty years earlier of the ultimate fate of a star. A dozen years after Ramachandran achieved his first rank, yet another illustrious young man from Presidency College, R. Chidambaram, had the distinction of securing the first rank among Physics Honors students. Chidambaram is a distinguished scientist who is currently the Chairman of the Atomic Energy Commission in India. In fact, Ramachandran's mentor, Sir C. V. Raman, also studied in the Presidency College, and was the youngest university graduate to also rank first among the physics honors students of his class. For once in so many years, Presidency College lost its distinction of producing the top–ranked student and in 1942 this honor went to our Ramachandran from St. Joseph's College in suburban Trichy. Talent exhibits itself early in life.

One of the most important legacies that the British left behind after three centuries of colonial rule in India was a sound system of education and a "good" administrative setup, although it has become an abominable bureaucracy. The so-called Indian Civil Service (ICS) consisted of a highly select and elite group of civil servants to carry on the routine administrative business of governing the vast country. The ICS was renamed the Indian Administrative Service (IAS) after the country achieved independence. Even today the officers of the IAS enjoy tremendous power and influence in the day-to-day administration of the enormous network of government departments. A principal goal of education among most Indians who could afford to go to school and college at that time was to enter the ICS or one of the other government cadres.

Like most educated fathers in middle class families, Narayana Iyer wanted his son to take the Indian Civil Service examination. At that time, before India became independent, this highly prestigious examination was administered in England and only very rich Indians could afford the trip abroad to take it. (Now, this examination is called the Indian Administrative Service examination and is administered in India by the Union Public Service Commission.) However, Ramachandran and his high school companion Ramakrishnan did not want to appear for the Civil Service examination. Both wanted to do research in science.

2. Bangalore–First Doctorate

Ramachandran's father, Narayana Iyer, failing to convince his son to take the Civil Service examination, sent him to Delhi to take an Indian Railway Engineering Service examination. A highly select group of students who passed this examination went on to study engineering for employment with the Indian Railways. Ramachandran hated this digression and deliberately performed poorly in the entrance examination so that he was not selected for the Railway service. The next choice for him in 1942 was to study for a master's degree for which he had already obtained admission in the Department of Electrical Engineering at the Indian Institute of Science in Bangalore.

Founded in 1911, the Indian Institute of Science has been a premier institution for science education and research in India, and 1942 was no exception. The following abstract provides a historical perspective on the Indian Institute of Science:

> The Institute was the brain child of Jamsetji N. Tata (1839–1904), a wealthy Parsi industrialist, who was convinced even in the 19th century India that the future progress of India depended crucially on research in science and engineering. Toward this goal, he envisaged a University as destined to promote original investigations in all branches of learning and to utilize them for the benefit of India.
>
> After consulting several authorities in India, J. N. Tata constituted a Provisional Committee to prepare the required scheme for the setting up of the Institute. On 31 December 1898, a draft prepared by the Committee was presented to Lord Curzon, the Viceroy-designate. The Secretary of State for India requested the Royal Society of England for an expert view, and the Royal Society requested William Ramsay, Nobel laureate and discoverer of the noble gases to help. He made a quick tour of India and reported that Bangalore was a suitable place for such an institution. In order to finalize the scheme, Lord Curzon took advice of Professor Orme Masson and Lt. Col. Clibborn of the College of Engineering, Rourkee, who had recommended Rourkee as a suitable area. However, on the initiative of Diwaan K. Sheshadri Iyer, the government of His Highness Krishnaraja

> Wodeyar IV, the Maharajah of Mysore, came forward with an offer of 372 acres of land, free of cost, in Bangalore and promised other necessary facilities. Thus the original scheme of Jamsetji Tata became a tripartite venture with the association of Government of India and the Maharajah of Mysore. The report that emerged recommended that the Institute be devoted to experimental science and aimed at training students in experimental methods; carrying out original research and discharging the functions of an accepted authority and referee on all scientific problems arising within its own domain.
>
> Early in 1911, the Maharajah of Mysore laid the foundation stone of the Institute, and the first batch of students were admitted to the departments of General and Applied Chemistry under Norman Rudolf and Electro Technology under Alfred Hay. The architecture of the main building, which today houses the administration and the Faculty Hall, is in classical style, carried out in gray granite and is crowned by a handsome tower which has become one of the landmarks of Bangalore. In front of it stands the work of Gilbert Bayes, a noble monument erected in memory of J. N. Tata. At its feet is an inscription which will serve to remind future generations of the generosity of Jamsetji Tata and the persistence with which he worked for the welfare of India (Indian Institute of Science, 1994-95).

When Ramachandran joined the electrical engineering department of the Indian Institute of Science, Professor Sir Chandrasekhara Venkata Raman, well known as Sir C. V. Raman, was the head of the Department of Physics. A very powerful figure in science in British India, Raman was internationally recognized for his classic work on light scattering. Raman had been awarded the Nobel Prize in Physics in 1930 for his work and the discovery of the so-called Raman effect. Raman had previously conducted his research work at the Indian Association for the Cultivation of Sciences in Calcutta

Raman left Calcutta and came to Bangalore as director of the Indian Institute of Science and also to start the Department of Physics. He was a highly controversial director and after serving one three-year term was asked to step down as director but continue as professor of physics. During Raman's time as director, the Indian Institute of Science was at its lowest ebb. All departments were neglected except the Department of Physics which of course was Raman's empire. Rumor had it that students joined other departments for a master's degree and used the excellent Institute's library facilities to prepare for the Indian Civil Service examinations. There were indeed exceptions: Vikram Sarabhai, who later became a pioneer in space research, was a student of the Institute, and Homi Jehangir Bhabha, the founder of the Atomic Energy program in India, was a faculty member. Both were in the elite physics department of C. V. Raman.

Needless to say Ramachandran was not very happy in the electrical engineering department and met Professor Raman every evening and pleaded with him for a transfer to the Physics Department. Having seen his record of achievement in physics honors, Raman too was keen on having Ramachandran as his student.

Professor Ramaseshan, a scientific contemporary of Ramachandran, describes in an article in *Current Science* the circumstances of Ramachandran's transfer to Raman's department as follows: "Not to offend the acerbic head of the electrical engineering department, Raman met him and requested the transfer [of Ramachandran to the Physics Department]. When this was persistently refused, Raman in his characteristic way said, 'I am admitting Ramachandran into my department as he is a bit too bright to be in yours.'".

Ramachandran describes his entry into Raman's lab in this way: "There was a friend of mine from St. Joseph's College, who had obtained first rank in the previous year, one P. S. Hariharan in the geology department [of the Indian Institute of Science]. He asked me to come to Bangalore, and even allowed me to stay with him. I joined the electrical engineering department, but wanted to work with Professor Raman, and so went and talked to Raman. He said I should write to my father before changing over from electrical engineering to physics. Finally he took me into his department."

This was the beginning of an extraordinary and remarkable career in science. Before actually starting his research for a doctoral degree in physics, Ramachandran had to obtain a master's degree in science and be nominated as an associate of the Indian Institute of Science. A master's degree was awarded on the basis of a thesis submitted after doing research. An associateship was a prerequisite for financial support during one's doctoral research. The research career of Ramachandran thus began in 1942 under the guidance and watchful eyes of C. V. Raman, who became one of his role models. This training and experience had a lasting influence on the life and science of Ramachandran.

Raman strongly believed that it was possible to do good science in India, despite the economic conditions and lack of adequate equipment. In fact, he himself began his scientific career while working as a senior government administrator in Calcutta, when he had accidentally discovered an organization called the Indian Association for the Cultivation of Sciences. He resigned his lucrative government job, joined and revitalized the association, collected a few good scientists, did experiments on light scattering using homemade equipment, discovered the Raman effect, and won the Nobel Prize for that work. The type of science and the equipment used had of course changed by Ramachandran's time, yet he followed Raman's practice and conducted all his research in India. He trained a large number of students just as Raman did.

Ramachandran is easily the most distinguished students that Raman produced. He describes his own life with Raman as follows: "Raman knew that I understood principles of optics. He gave me a very important problem. Consider light scattered by various planes separated by 4, 5, 6, . . . 10 millimeters and so on. It is actually Bragg diffraction. Consider reflection from one plane, reflected back from the next plane and so on, known as multiple reflections. This problem had been treated earlier by Raleigh-Jeans. Raman gave me Raleigh's paper and a book pertaining to this problem. In one day I was able to write the equation to the problem and work out the solutions. I was horrified to see the solution containing several hyperbolic sines and cosines. I had seen it before and I went to the library and found this volume with several formulae and equations. I was very pleased to find completely corresponding equations and solutions in that book. I wrote a very rigorous proof and showed it to Raman. He was so pleased. He said we should publish the results, this was within one week of my joining Raman. That was a very useful result, which I used twenty years later in studying crystal perfection and the difference between mosaic and perfect crystals."

"Raman recommended me for a scholarship of 60 rupees a month. But the administrators of the Institute said that I had to have a master's degree. There was some confusion between a B.Sc. with honors conferred on students from North India and the B.Sc (Honors) degree from

South India, the latter was equivalent to a master's degree. Raman said, 'Don't worry about it, I will give you a fellowship of 130 rupees a month, you get an associateship degree from the Institute.' There were no courses to take, only research. The degree awarded was called A.I.I.Sc. I was in charge of setting up an X-ray diffraction unit, it was a demountable X-ray tube.

"In the Institute I used to give lectures on crystallography, starting with symmetry. I studied crystallography all by myself. I studied a book on group theory, and it became very useful throughout, particularly in my work on logic. There were very few books on group theory and this book was by Herman Weyl. That changed my whole attitude to science.

"Raman had great respect for students who were better than him in mathematics. He gave me another problem to study the scattering of light by small particles, 3 or 4 times the wavelength of the radiation used.

"Raman had ten to fifteen students working under him. He was a virtuoso, and each student was working on a different problem. Raman tried to bring famous scientists from abroad and he even tried to get a faculty position for Max Born, who was a visiting professor in his department. He wanted Erwin Schrodinger to come to India. This was a time when many scientists were leaving Germany. At that time Raman was the director of the Institute, but after the first three years, the administrators of the Institute told him: 'We don't want you'."

The thesis that Ramachandran submitted for the master of science degree was titled "Optics of Heterogeneous Media." It was submitted to the University of Madras. In those days the Indian Institute of Science was not a degree–granting institution, students had to submit their theses for a degree from one of the other universities in India.

Ramachandran's thesis embodied the results of the theoretical and experimental investigations he carried out on the propagation of light through optically heterogeneous media. The thesis contained six chapters on topics varying from the theory of diffraction coronae to the transmission of light through a cloud of particles, the optical theory of chromatic emulsions, and reflections by periodically stratified media.

A summary of results contained in each chapter is presented in Appendix I. It is taken directly from Ramachandran's M.Sc. thesis.

Ramachandran concludes the introduction of his thesis as follows: "I wish to express my sincere gratitude to Professor Sir C. V. Raman for the kind and encouraging guidance he gave me during the course of these investigations. All the problems were suggested by him, and I am particularly indebted to him for the many discussions I had with him."

Ramachandran obtained his master of science degree in 1944 from the University of Madras. The rules of the university stipulated that the thesis, even for a master's degree, had to be evaluated by an outside examiner, that is by someone from a different institution. The outside examiner had to send his or her report directly to the vice chancellor, the chief executive officer of the university. The rules also stipulated that the report was not to be given to or seen by anyone else, including the research supervisor of the student. The vice chancellor was to read the report and decide if the thesis could be accepted and a degree awarded: all this for a simple master of science degree!

In Ramachandran's case the external examiner for his thesis was none other than Professor Sir K. S. Krishnan, professor of physics at Allahabad University who had worked with Raman on the Raman effect. Krishnan later became the first director of the National Physical Laboratory in New Delhi, one of the premier national laboratories in independent India. Commenting on Ramachandran's M.Sc. thesis, Krishnan is supposed to have written in his report that "the thesis was worth at least two doctoral degrees!" In Ramachandran's own words: "I personally was not worried about what the comments were in Sir K. S. Krishnan's report. Students do not get to see the report anyway; they would not even show it to Professor Raman. But my father wanted to see the comments. Since he knew the registrar of the university, once after a meeting of the University's Syndicate [the policy–making body of the University], in which he was a member, he asked to see the comments of a thesis which he said was submitted by his son. My father was absolutely thrilled on reading the comments."

Having obtained his master's degree, Ramachandran continued his research work for a doctoral degree in Raman's department. There were two types of doctoral degrees granted by Madras University at the time: one was the doctor of philosophy or Ph.D. It was awarded for research work carried out by a student under the supervision of an approved mentor. In this case the supervisor suggested the research project and monitored the student's progress. The second degree was a doctor of science, or D.Sc. This was awarded to students for what was considered independent and original research work. The supervisor's role was to provide necessary laboratory facilities for the research and any intellectual or scientific discussion on the research project. A thesis for the D.Sc. degree usually consisted of a collection of independent research publications written by the candidate and published in reputable and refereed science journals. Ramachandran's work belonged to the latter category and in 1947 he submitted his thesis, for which he was awarded D.Sc. degree in 1948 while at Cambridge. The thesis contained all the research work he conducted on his own in Raman's department. Lord Raleigh, one of the most famous British physicists of the time, was an external examiner of his doctoral thesis.

Ramachandran's doctoral research involved photo-elasticity and thermo-optic behavior of different solids such as diamond, fused quartz, fluorspar and zinc blende. Among the studies in this early period was his work on what are called X-ray topographs of diamond: a picture that showed the variation in perfection over the surface of the crystal. Ramachandran's publications in 1944-1946 contain some of the earliest applications of X-ray diffraction to the study of variations in perfection of crystals. The name *topograph* for such pictures was introduced and adopted for the first time by Ramachandran in these papers. The thesis also contained original results on the theoretical calculations of optical rotation of crystals, such as quartz and sodium chlorate, from their crystal structures. All of Ramachandran's scientific publications of this period carry his name as the single author. Curiously, Ramachandran does not have a single publication in which he is a coauthor with Raman.

Ramachandran's reputation as an outstanding graduate student in Raman's department had spread all over the Institute. According to Ramaseshan, "The following is an example to illustrate the ease with which Ramachandran could absorb ideas when the slightest mention was made to him and how with lightning speed he could implement them. I vividly remember when Raman told Ramachandran that he [Raman] had observed non-uniformities inside Laue spots. He thought that they must be due to variations in the reflecting power of the crystal and felt that it should be possible to get a point–to–point mapping of the imperfections in a diamond plate. This took place on a Friday evening before Raman left for his country estate to spend the weekend. By the following Monday morning Ramachandran had not only worked out the theory and the experimental arrangement, but had actually obtained excellent topographs of a diamond plate."

Among Ramachandran's colleagues in those early days in Bangalore were several bright young students who met in the evenings at each other's dormitory rooms or houses to discuss a variety of topics. No topic was excluded from such discussions. Subjects included politics (India was about to get its independence from the British), science (the group included students of physics, chemistry, microbiology, and mathematics), and music (almost everyone was a connoisseur of classical Indian music). All the participants in that group became distinguished and prominent scientists in their respective fields, including S. Ramaseshan, who later became the director of the Indian Institute of Science; S. Swaminathan, who became a professor of organic chemistry at the University of Madras; and Jagannathan, who retired as one of the deputy directors of the National Chemical Laboratory in Pune.

In 1945, Ramachandran married Ms. Rajalakshmi, also known as Rajam. Rajam's family hailed from a village called Tharuvai in the district of Tirunelveli, close to Gopalasamudram and also in the same district as the hometown of Ramachandran's parents. Neither Ramachandran nor Rajam have actually lived in their native village. Rajam's father was a senior railway engineer and worked in different parts of North and South India, and therefore Rajam had her education in both regions. Rajam had just finished high school when her parents began planning her marriage.

Their marriage was a traditional one arranged by both sets of parents. Rajam lived with her parents in Nagpur in Central India, Ramachandran's parents lived in Ernakulam in South India, and Ramachandran was a graduate student in Bangalore. Rajam's parents received three proposals: one from the family of an officer in the Indian Civil Service; the second from an engineer in the Railways; and the third from this graduate student in the physics department of the Indian Institute of Science. The standard practice was to have a professional astrologer match the horoscopes of each boy and the girl. In this case, the civil servant and the engineer were ruled out by Rajam's parents; everyone agreed that the physics graduate was the one to choose as "he was very bright and came from a highly respectable family".

Ramachandran's father was anxious to fix a date for the marriage even before the bride and the groom met. However, Rajam's mother apparently said, ". . . not so fast, we want the boy and the girl to meet and see each other". Traditionally, the boy goes with his parents or other members of his family to the girl's house for a prearranged social get–together. The boy and the girl see each other in the presence of other family members. Very soon thereafter the families communicate their decisions to one another. If both agree to the marriage, the date is fixed and any dowry to be exchanged is usually negotiated at that time.

In this case, the tradition was broken. Rajam went with her parents to Bangalore, where they stayed with relatives. A meeting was arranged for Ramachandran to meet Rajam in the presence of other family members. Everyone agreed to the match, and the marriage was held in 1945 in the city of Madras where Rajam's father had an influential friend who could help in making all the necessary arrangements. Because World War II was in progress and there was strict rationing of most essential commodities, this friend's help was highly appreciated.

The newly married couple did not start living together immediately after the marriage. Rajam continued to stay with her parents in Nagpur and went to college for one more year before joining Ramachandran in Bangalore. Arriving in Bangalore, Rajam wanted to continue her college education, but Ramachandran's mother apparently said; "My son is going to bring any number of degrees, you don't have to get one too."

Rajam was the most important and most influential companion in Ramachandran's life. She was an extraordinarily remarkable woman, full of energy, enthusiasm, kindness, and magnanimity, and she kept the family together in difficult times. It may not have been easy being the wife of a well-known scientist, but she charmed and made a lasting impression on everyone who met her and became acquainted with her.

In 1947 Ramachandran submitted his doctor of science thesis from the University of Madras for research work he carried out in Raman's laboratory at the Indian Institute of Science. That was also the year India became independent after three hundred years of British rule. However, independence after such a long time left India in total disarray and presented numerous problems. The country needed large number of scientists, engineers, and other skilled personnel, so that it could begin to build its infrastructure, modernize its industry, and compete with other developed nations of the world.

Economically India was in ruins. The majority of people lived in villages and most of them were extremely poor with very low standard of living. Religious riots occurred all across the country; thousands of Hindus and Moslems were slaughtered in the name of religion. In the midst of this turmoil, Jawaharlal Nehru, the first prime minister of free India, and his government arranged for young scientists and engineers to go to Europe, Great Britain, and the United States for higher education and training. It was hoped and expected that they would return to India and provide the leadership needed to build a new modern India. This was essential if India was to stand on its own feet, improve the standard of living, and become a technically advanced nation.

3. Another Doctorate From Cambridge

It was not unusual for outstanding scientists to go abroad under some scholarship or fellowship to obtain exposure at renowned centers of research. There were a few highly prestigious fellowships such as the Rhodes Scholarship and the 1851 Exhibition Scholarship. It was under one such scheme that Ramachandran went to Cambridge in October of 1947 to continue his education. He was successful in getting a prestigious fellowship, provided by the Royal Commissioners of the 1851 Exhibition. Following the highly successful exhibition held in Earl's Court in London in 1851, the commissioners of that exhibition set aside funds to provide for the training of outstanding and promising young scientists from the former British Colonies in universities in Great Britain.

Ramachandran decided to go to Cambridge in England, and work in the famous Cavendish laboratory where Sir William Lawrence Bragg was then director. Bragg discovered the principles of X-ray diffraction and was a pioneer in the determination of crystal structures of inorganic compounds and minerals. He was also about to launch with Max Perutz and John Kendrew the X-ray structure analysis of macromolecules. Since Ramachandran had already studied X-ray diffraction for his doctoral research in the Indian Institute of Science it was easy for him to become a part of the Cavendish group of crystallographers. He was slightly disappointed that he could not work directly with Sir Lawrence Bragg, as he was assigned to work with Dr. W. A. Wooster, a junior faculty member of the laboratory. Another young scientist, Andrew Lang, was also working in Wooster's laboratory where he was constructing Geiger counter circuits for detecting X-rays.

There was no question of Rajam accompanying Ramachandran to England due mainly to the enormous travel costs and living expenses. Ramachandran wanted his wife to join him during his second year, but somehow it just did not work out. It is interesting to note that Shankar Dayal Sharma, who later became the President of India, was a contemporary of Ramachandran, studying English literature in Cambridge and obtaining a doctoral degree from the same university.

Several years earlier, another famous Indian mathematician by the name of Ramanujan had gone to England to work with the famous Cambridge mathematician Thomas Hardy. Unfortunately, Ramanujan became seriously ill in Cambridge and had to spend a considerable amount of time in hospitals and sanatoriums. Though he returned to India as a Fellow of the Royal Society, he died a premature death as a result of his bad health which was attributed to malnutrition. Ramachandran's parents were aware of Ramanujan's story. It was well known at the time that Ramanujan's health problems resulted from the fact that he was a strict vegetarian. Most likely this prompted Ramachandran's father to advise him "to eat whatever he could get." This was unusual advice coming from an orthodox Brahmin, but Ramachandran followed it seriously and from the moment he set sail for England he did not mind eating non-vegetarian food. During his stay in England in the years immediately following World War II, there was scarcity of food in general and meat in particular. Even horse meat was being sold. It must have been repugnant for a vegetarian to go that extreme.

Ramachandran's mentor, Sir C. V. Raman, was not very much in favor of his proteges going to England or the United States to work for a second doctorate degree. In particular with Ramachandran, who had already obtained a prestigious doctor of science degree, Raman felt that there was no need to obtain a second lesser doctor of philosophy degree even if it was from Cambridge University. Raman also felt that good science could always be done in India without having to go abroad.

In Ramachandran's own words: "In 1947 I went to Cambridge, England, to work in the Cavendish laboratory with Dr. Wooster. Dr. Taylor was the head of the crystallography group. I did not attach myself to any college in Cambridge and I was in Fritzwilliams House. I did not like to wear those gowns like the ones the undergraduates were expected to do. I decided to work for a doctoral degree because then there would be something concrete to show for my work; simply getting a few publications does not impress authorities in India. My decision may have definitely helped me in getting my first job in Madras, as Alladi Ramakrishnan was the only other candidate for the professor's job in Madras. Not only did he not have two doctorates like I had, he also had no teaching experience."

Ramachandran's research in Cambridge consisted of three different projects— instrumentation, electronics, and the development of a mathematical theory to study diffuse X-ray diffraction and use it in determining the elastic constants of crystals. This involved converting the Debye-Waller theory into a suitable form for use in studying diffuse reflections and measuring their intensities with a two-circle goniometer using a curved crystal monochromator. All three investigators shared this work. Dr. Wooster was in charge of the mechanical and instrumentation aspects of the project; Ramachandran converted the general theory of diffraction in a form suitable for diffuse reflections; and Andrew Lang was responsible for the electronic aspects of the counting circuits for detecting X-rays on the goniometer.

The theory led to a novel design for crystal setting to explore the intensity of a reflection at non-reciprocal lattice points. Because this was all Ramachandran's work, Dr. Wooster asked him if he could suggest a nice Sanskrit name for these points. Ramachandran suggested *Kiran* or *Rekha*, both meaning "ray" as in "ray of light", they eventually chose *Rekha* to describe the diffuse scattering. This is one example of Ramachandran using words from classical Indian language for specific entities or phenomenon in physics.

According to Ramachandran: "Going and staying for two years in Cambridge did a lot of good things for my research. I attended Dirac's course on Principles of Quantum Mechanics. I was taking notes in every lecture word for word, but then I discovered that everything that he was saying was in a book, so I bought a secondhand copy of the book and used that for the lectures. Most students in Dirac's class were undergraduates who were second–or–third year physics majors. He used matrices and tensors a lot. Later I used the same symbols in my mathematical treatment of logic. Whatever I tried to design for my experiments could not easily be implemented because there was no suitable engineering program in Cambridge University."

Following are copies of some personal letters written by Ramachandran to one of his close friends at the Institute, Dr. S. Swaminathan. Both were in the Institute in early 1945, Swaminathan obtained an associateship degree from the Institute at about the same time and went to the University of Illinois at Champaign-Urbana for his doctoral research in organic chemistry. Four letters written by Ramachandran to Swaminathan during the period 1947–1948 are available. Selected parts of those letters are reproduced here with their permission.

These letters provide the only available insight into Ramachandran's life in Cambridge. The letters were all handwritten in clear and beautifully legible English, a characteristic that Ramachandran has possessed throughout his life. There is no ambiguity or hesitation in his writing either in letters or scientific articles.

First letter dated 24 December, 1947:

Crystallographic Laboratory,
Cavendish Laboratory, Cambridge
24-12-1947

My dear Sama:

I am sure you will excuse me for not writing to you so far even though it is two months since I came here, when you have read through this letter. I got your reply even before I left Bangalore. However I lost the letter along with a nice leather wallet at Southampton, so please excuse me if I am not able to answer anything specific you have asked in it.

I came to England on 23rd October. The voyage was quite uneventful. We had glorious weather all throughout the voyage and the sea was perfectly calm except for the last day. I joined the University here on 25th October. I am sorry to write to you that I am not at all happy in my work here. The Cavendish lab is supposed to be the best lab for Physics in Gt. Britain. The facilities are quite good, but I have been very much restricted by the fact that I have to work on a particular problem with a particular person. I do not know why it happened. Usually here a student on joining is asked to choose his own line of work. Anyway I am trying to make the best of what is available. As a result, I have not been in a mood to write to anybody. I however decided to write to you now because I was afraid you might be very angry with me otherwise. . . .

How are you getting on? Please write to me in detail about your work. Are you working on stereochemistry or some other branch? Did you try the cyclohexanone problem? What happened to the Paludrine patent? Did you succeed in America about it? Please write to me about everything. Have you made friends with a number of Americans? I find it very difficult to do so with Englishmen. It is very easy to talk to a foreign student, but not so with English students. I thought that I was to blame in this matter, but from my conversation with others, I find that they too find the same difficulty. There are some 60 Indian students here doing research and studying for tripos. Many of them are for arts. Bengalees form the maximum number among the various provinces. But there are three women students from Madras. I have not met any of them so far—out of the seven Indians. Cambridge University is very fine; the whole town has a very cultured atmosphere. Compared with London & other provincial towns Cambridge is very quiet & free from the bustle of factories and so on. The strict formalities of English customs are not at all to be found here. I go to the lab in a gray flannel pants, sports coat and a sweater & many go about with corduroy pants of outrageous colors—bright yellow for instance. The atmosphere in the lab is very good in general, & I find that students are at perfect liberty to work as they like. At meetings and colloquia, the professor is not given any special respect & all take part in the discussions without any restriction. (Unfortunately for me, the person with whom I am working is somewhat different and I have to play second fiddle to him, although I do not find that he knows much more about the subject than I do.) The meetings are very informal & I have seen some sitting on desks, or going out in the middle if they are bored or have some work to do outside.

I hope you have got some letters from Ramaseshan recently. Please excuse me if I have written all about myself in the letter. I cannot help it. I sometimes wonder whether Professor Raman was not right in advising me not to come here. I wish to try and manage to get my scholarship available outside Britain for next year. How much do you spend on the average in your place? . . . I have sent my D.Sc. thesis to Madras before I left Bangalore. Please write to me early although I have been rather late in replying to you . . . .

If you have published anything, please send me reprints,

Yours affectionately,
G. N. Ramachandran
Jai Hind*

While in Cambridge, Ramachandran had the opportunity of meeting Linus Pauling for the first time. This meeting was very significant for

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*This is a form of salutation meaning "Glory to India".

Ramachandran. Three people influenced his scientific thoughts and his entire career in science: Sir C. V. Raman, Sir Lawrence Bragg, and Linus Pauling. Ramachandran's vision of chemistry had been molded by reading Pauling's books and articles on chemical bonding. For a young Ramachandran of 25 years, Pauling was a hero whom he immensely admired and even glorified. In fact his admiration of Pauling has continued unabated throughout his life. Pauling had just discovered the alpha helical structure of polypeptides and he had come to Cambridge on a lecture tour. The discovery of the alpha helical structure by Pauling was an important milestone in molecular biophysics, and a personal disappointment for Sir Lawrence Bragg who was also working on structures of polypeptides. The main reason Bragg missed discovering the alpha helix has been attributed to the fact that he did not utilize the chemical evidence of a planar peptide bond as seen in the structures of several small di– and tripeptides. Bragg was also unaware of the possibility of non-integral helical structures for polypeptides.

Ramachandran was working toward a second doctoral degree in Cambridge and discussed with Linus Pauling the possibilities of going to California Institute of Technology (Caltech) in the United States, where Pauling was a professor of chemistry. Apparently the last date for submitting applications for fellowships had expired for that year and Pauling asked Ramachandran to apply for the fellowship the following year. This never materialized and one wonders how Ramachandran's life would have changed if only he had decided to go to Caltech to pursue his ambitions!

While in England as a graduate student, Ramachandran visited the United States to attend a conference on crystallography at Harvard University in Cambridge, Massachusetts. Ramachandran's second letter to Swaminathan in Illinois throws considerable light on his life in Cambridge and his arrangements for the trip to America. It also shows glimpses of Ramachandran's sense of humor, his love for the game of cricket, and his relations with his research advisor in Cambridge. Excerpts from that dated 22 June, 1948 follow:

1 St. Clements Gardens
Cambridge
22-6-1948

My dear Sama:

I was delighted to get your reply so soon. Thank you very much for all the information. I am making some arrangements here regarding the return passage (from USA), but no success so far. I would like you to do the following for me. Ask the travel agent to book me a passage to England or to any country in Europe like Sweden, Holland, or France anytime between 10th and 20th of August; if impossible the earliest after 10th August. If they can, let them also arrange the journey from Europe to England. If difficult I can do it here. Please ask them to write to me c/o Cavendish Lab, Cambridge by air mail as soon as they fix the passage, so that I can arrange to get the money paid here in Sterling, get visas to the countries in Europe etc. I do not still know when I am sailing, but most probably it will be between 10th and 20th July. If the American Express Co. can do anything, please ask them to cable to their London Office at 6 Haymarket, London S.W.1 regarding it, as they are trying to arrange the return journey for me. It will be much more pleasant for me if I can be definite of the return even when starting from here. That is why I am cursing the India Office at London.

Regarding the money, you need not worry as I can get my cheques converted into traveller's cheques through a bank in London. They have written that they can do it & I intend going there in 3 days time. I shall write to you and to Patnaik as soon as I know the ship in which I am sailing. I learn from here that all the ships from New York to this country have been booked up to end of September. So it is better to try some ships going to the continent of Europe. Please make this clear to the travel agents when you write to them.

I am very glad you hope to come to Harvard and that we can meet. It will be really very nice. For some reason, I feel that it is two years since you left Bangalore. That is why I asked you if you have finished your Ph.D. I do not know how you like preparing for exams and so on after three years spent on doing research. As for myself, I am not so bad as you seem to have got the impression. When I wrote my last letter I was in a very depressed mood and probably that explains it. I am working as one of a group of three. We are planning a rather elaborate experimental setup and it has taken nearly eight months to make it. Just now I have started taking readings and it appears to work well. So I hope to turn out some work when I come back from the visit to the U.S.A. My own coworkers are extremely nice to me. I had a wrong first impression of Dr. Wooster, the leader of our team. He is a nagging type of person, but he is very good at heart, so that one has to overlook his peculiarities. So far I have published one independent paper in the *Acta Crystallographica* & 2 others (joint) have been sent to the *Journal of Scientific Instruments*. By the way, since I wrote to you last, I have got my D.Sc. It has taken 10 months for the results to come. The examiners were all from this country. G. P. Thomson was chairman.

I met Nambeesan in December. He finds the lab not well equipped and he has not progressed much with his Ph.D. He hopes to finish the work by the end of this year. I may meet him when I go to London this week. I shall give him your best wishes. He too has not written to me although I wrote twice to him. Otherwise he is getting on very well indeed. He is quite happy. I gave him your address in December. R.C. Narayanan is in Manchester doing work on electron microscope. I met him there. He has not changed at all, unlike Nambeesan. More of all these when we meet.

What is Jagannathan still doing in Stanford? Has he become so fond of America that he wants to stick there? Did I write to you that I got a letter from Chandru a month or so ago? No letters from Ramaseshan as yet. I hope he will at least write congratulating me on my doctorate. The second test at Lords begins day after tomorrow. My lab closes on Friday for a week so that I may go to see the match. It all depends on the India House. Still they have not fixed the forward passage for me.

I am playing cricket regularly here & I am one of the good bowlers of the Cavendish Lab—doesn't speak highly of the Cavendish Cricket team, does it? Otherwise life is very dull here. I work hard so that I do not feel bored. I shall write to you again as soon as I know when I am sailing. If you have any success with the shipping agents please write to me immediately. Rest in person,

yours affly,
Ramachandran

Ramachandran sailed to America on the *Queen Elizabeth* and visited New York, Princeton, Washington, D.C., and Harvard. He attended the First International Crystallographic Conference at Harvard in 1948. It was the first of many international conferences which Ramachandran participated for years to come.

Additional glimpses of Ramachandran's research and his doctoral thesis may be seen in his fourth letter to Swaminathan written in 1949 from Cambridge, England. Here are some excerpts:

1 St. Clements Garden
Cambridge
20/2/1948

My dear Sama:

It is a very long time since I heard from you. In fact I have not received any letter at all from you since I met you at Cambridge (U.S.A). I hope you are getting on well. You must have finished your exams by now & must be devoting yourself wholly to research work. I am sure you must have done brilliantly in the exams.

What problem have you taken up? When do you expect to finish the work? By the way, did you do anything at all about the paludrine after our talk about it? Have you got the patent in India? I am dying to hear from you about everything.

As for myself, I think I have some brighter news to write. My work has gone on surprisingly well after my return from U.S.A. and I hope to be able to submit my thesis for Ph.D. by June, if everything goes well. As you may know already I am working on diffuse reflections of X-rays. In collaboration with Dr. Wooster, I have now evolved a new method of determining the elastic constants of crystals by the study of diffuse reflections. In this method the crystal need not be subjected to any strain at all. What we measure is in effect the velocities of the thermal waves existing in the crystal in the form of thermal energy & calculate the elastic constants from them. I think I am boring you with all this.

Have you received any letters from friends in India? I had a letter from Ramaseshan recently, because I wanted a specific thing to be done by him. He has profoundly apologized for not writing to me and says that it is only due to laziness and nothing else. I heard from Chandru that Ramaseshan has been appointed temporary lecturer in the Physics department. I have no idea at all as to how the department is getting on under the regime of Dr. Krishnan.

How was the winter in Urbana? Here so far it has been quite mild. There has been no snowfall in Cambridge till now. I must say I have been lucky in having two successive winters which were not cold.

That reminds me, what became of my colour photographs which I gave for development at Cambridge Mass. Were they sent to you? Have they come out well? Don't worry if you can't send them over to me by post. However, I would like to know if at least some of them have come out well. What happened to your photographs? If they are good, please send me a copy of each.

The last time I heard from Nambeesan was some 4 months ago. Then he was writing his thesis & was to have submitted it by December. I don't know more about that.

Please write to me a detailed letter as early as possible. Hope this finds you in the best of health and cheer.

Yours affly
Ramachandran

During his two years in Cambridge, Ramachandran designed experiments in X-ray diffraction which later found application in neutron diffraction. From classical physics he worked out a formula for the diffuse reflections of neutrons that not only led to a variation in the direction of the diffused ray, but also led to a change in the momentum. Ramachandran saw the unique possibility of applying the concept of coherent scattering with change of wavelengths and frequencies in the case of neutron scattering. He realized that this was the analogue of the Raman effect in the theory of neutron diffraction. Ramachandran worked out the relevant formulae from De Broglie's celebrated equation for the relation between wavelength and momentum of a neutron beam, namely $\lambda = h/mv$ or h/p.

While Ramachandran was working out these ideas on neutron scattering an interesting episode occurred. There was a seminar on quantum mechanics and particle physics by Professor Werner Heisenberg, famous for the uncertainty principle. Professor Heisenberg was staying in Cambridge for a week or two after the seminar. Ramachandran wrote a two-page report of his ideas on neutron scattering and went to see Professor Heisenberg in his office. Heisenberg read through the summary and was astonished that these ideas, which were at the frontiers of theoretical physics, were put forward by someone who was not only a Cambridge graduate student but came from a developing country like India. After first congratulating Ramachandran, Heisenberg told him, "Young man, your paper is interesting, but you are one year too late." Presumably it had been worked out earlier and Ramachandran, not having worked actively in that field was not aware of those results. Nevertheless, he had thought of it on his own—completely independently.

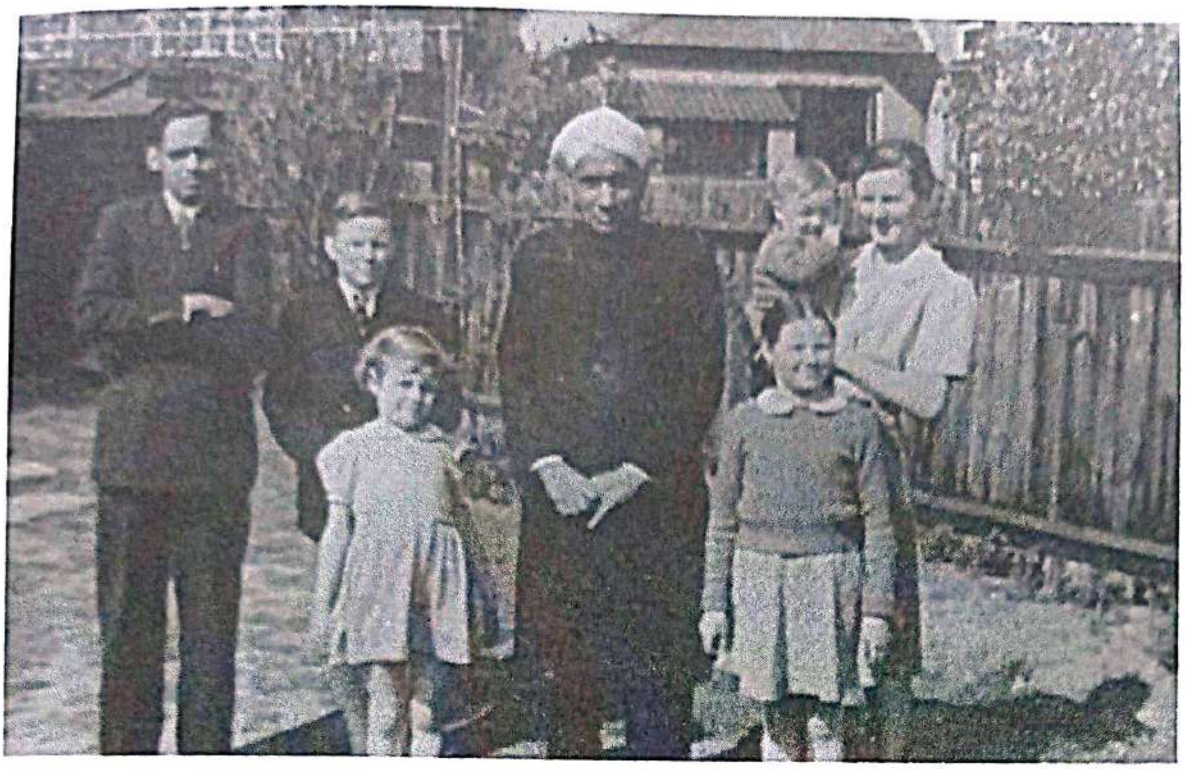
Aside from science, Ramachandran found the cultural and the intellectual atmosphere in Cambridge highly rewarding. Andrew Lang introduced him to Western music and they both enjoyed classical music. Together they attended several chamber concerts. Ramachandran got so interested that he bought a used gramophone and started collecting a set of records of western music he had heard on the BBC.

During the summer of 1948, Ramachandran went on a guided tour of Edinburgh and its environs in Scotland. The British Council had arranged the tour for visiting students from the Commonwealth countries. Ramachandran selected a tour that included attending a play and a violin concert by the famous Yehudi Menuhin. This concert produced a lasting impression on young Ramachandran and he bought a large collection of Western classical music. This interest has continued throughout his life and all his children have also developed a great taste for Western classical music, in addition to traditional Indian classical music.

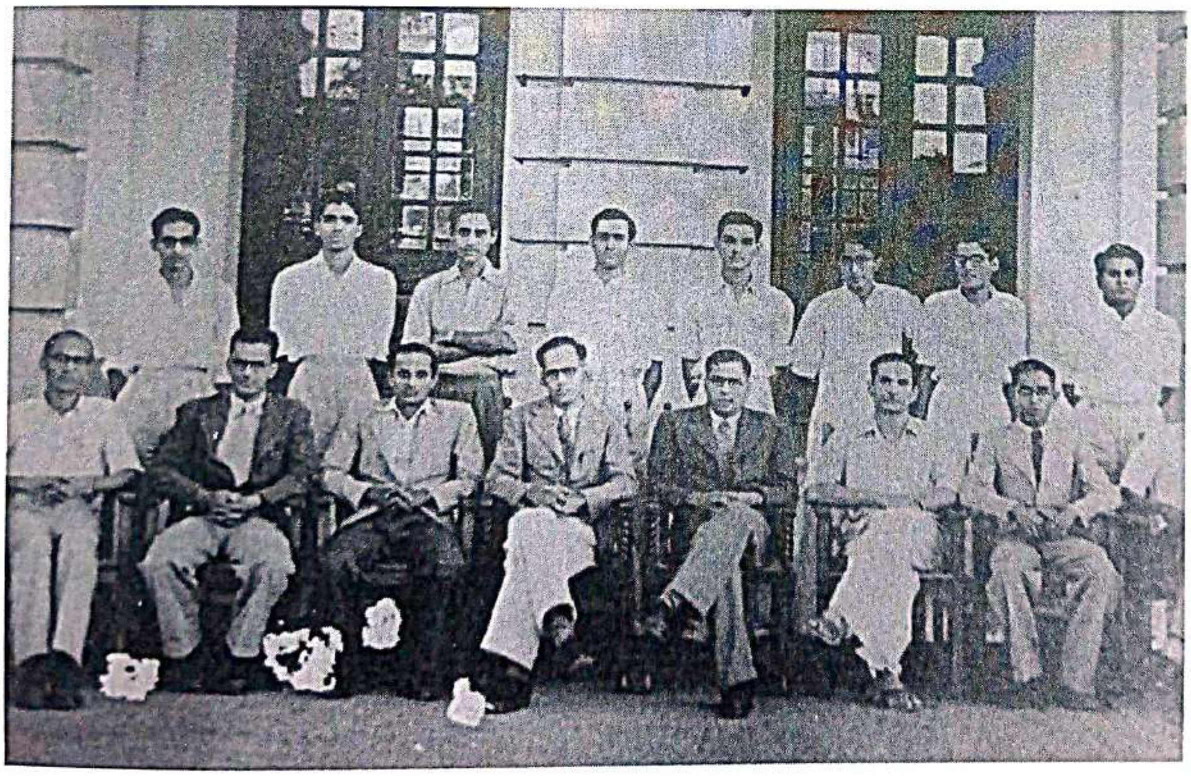
Another lucky opportunity came to Ramachandran when he noticed an announcement on a bulletin board at the Cavendish laboratory that the well–known Dutch philosopher Professor L. E. J. Brouwer was giving a seminar on the principles of not excluding the third truth value of a logical statement. He went to the seminar, which created such a lasting impression on him that fifty years later he worked out the Boolean Vector Matrix Formulation as an unavoidable consequence of a standard two valued state for logic.

Ramachandran's Ph.D. thesis was submitted in May 1949 to the University of Cambridge. It took less than two years after he came to England and started his research work to complete his doctoral thesis. Even for Cambridge University this must have been a record. Obviously, it was possible because Ramachandran did not have to do any course work since he already had a doctoral degree from India. His handwritten thesis was titled "Determination of Elastic Constants of Crystals from Measurements of Diffuse X-ray Reflections." Ramachandran says, "There was no time to get the thesis properly typed and bound, so we bought a few high–quality binders, put the thesis in it, and submitted it to the University." This research was done in collaboration with W. A. Wooster and A. Lang. He thanked W. H. Taylor and W. L. Bragg for encouragement, and he acknowledged the Research Scholarship awarded to him by the Royal Commissioners for the Exhibition of 1851.

He was only 27 years old and he had two doctorate degrees, one from Bangalore, India, and another from Cambridge, England.

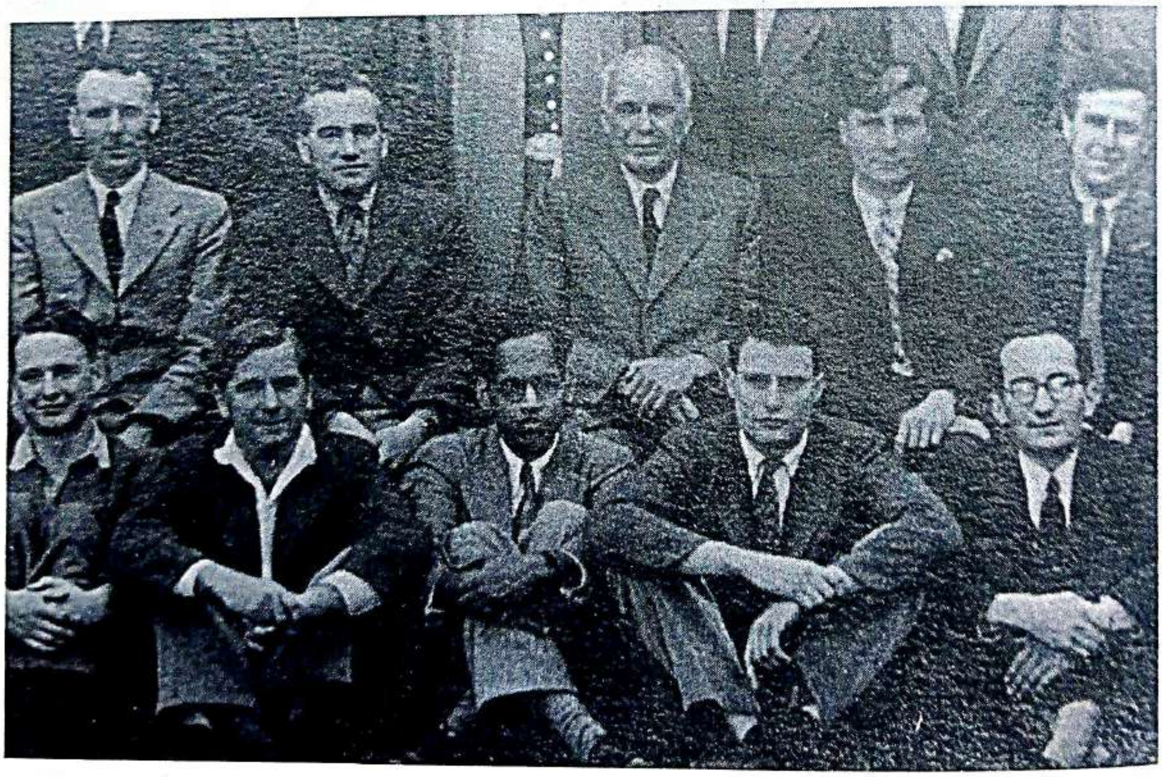


1: A group photo of Ramachandran (far left) taken in Cambridge, England with his host family when his mentor, Professor Sir C. V. Raman (fourth from left) visited him in 1948.

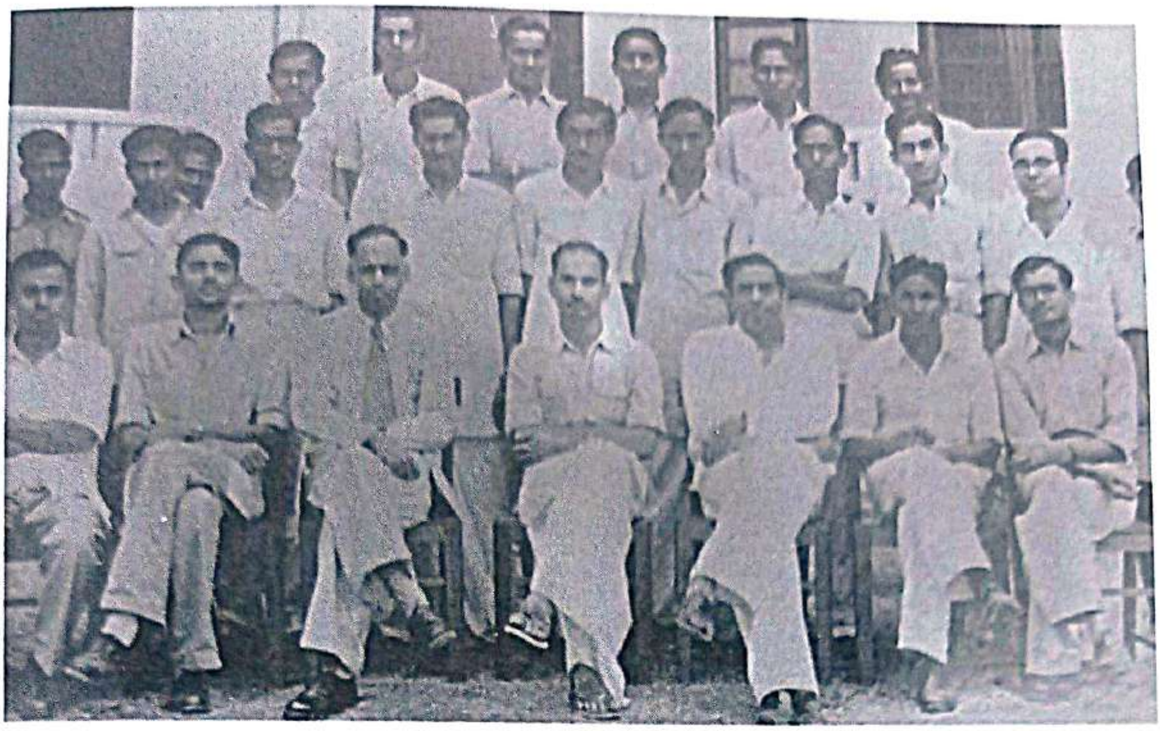


2: A group photo taken in the Physics Department of the Indian Institute of Science, Bangalore after Ramachandran joined its faculty as an Assistant Professor in 1949. Seated in the front row are S. Ramaseshan (third from left), G. N. Ramachandran (fourth from left) Chairman of the Department, Professor R. S. Krishnan (fifth from left) and Dr. G. Kartha (third from right).

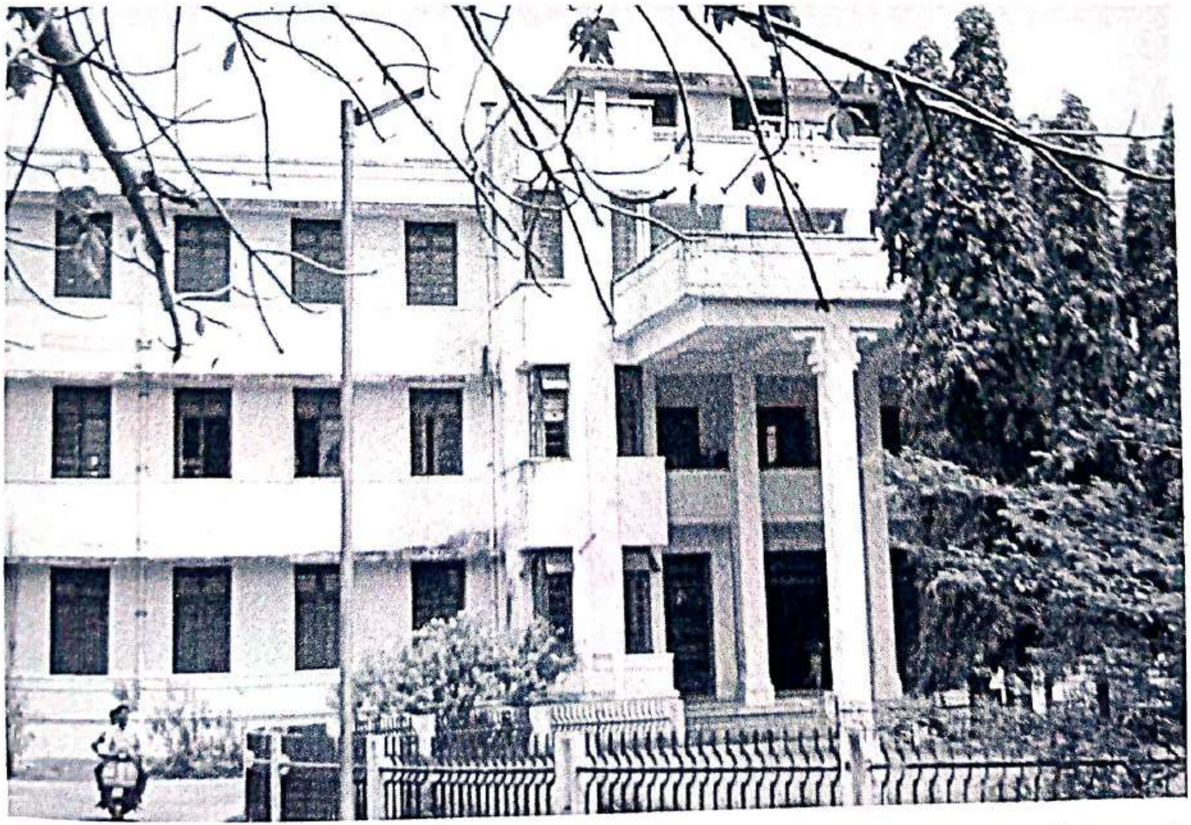
3: Maharaja's College, Ernakulam, where Ramachandran had his early college education. His father was the Principal and a Professor of Mathematics in the same college.



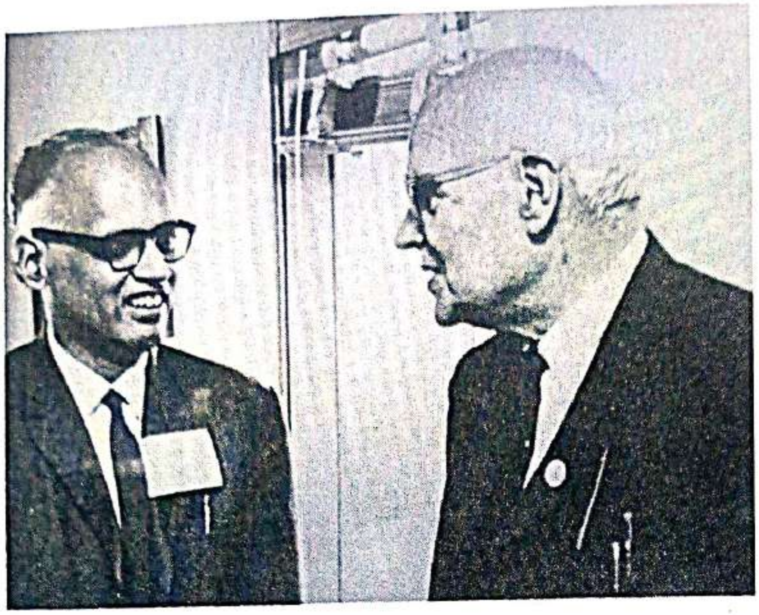
4: A group photo taken in the Cavendish Laboratory in Cambridge, England in 1948 when Ramachandran was a student (seated on the floor, third from left). He was doing research in Dr. Wooster's laboratory for a second doctorate degree. Sir Lawrence Bragg was the Director of the Laboratory (seated third from left).



5: A group photo taken in 1952 showing the members of the newly created Department of Physics at the University of Madras. Seated in the first row from left to right are: M. A. Lonappan, K. S. Chandrasekharan, G. N. Ramachandran, G. Kartha, Allady Ramakrishnan, P. M. Mathews and M. S. Santhanam. Standing in the middle row are R. Srinivasan (fourth from left), and E. V. Krishnamurthy (fifth from right). Standing in the top row are S. Raman (first from left), G. K. Ambady (second from left) and V. Sasisekharan (second from left).

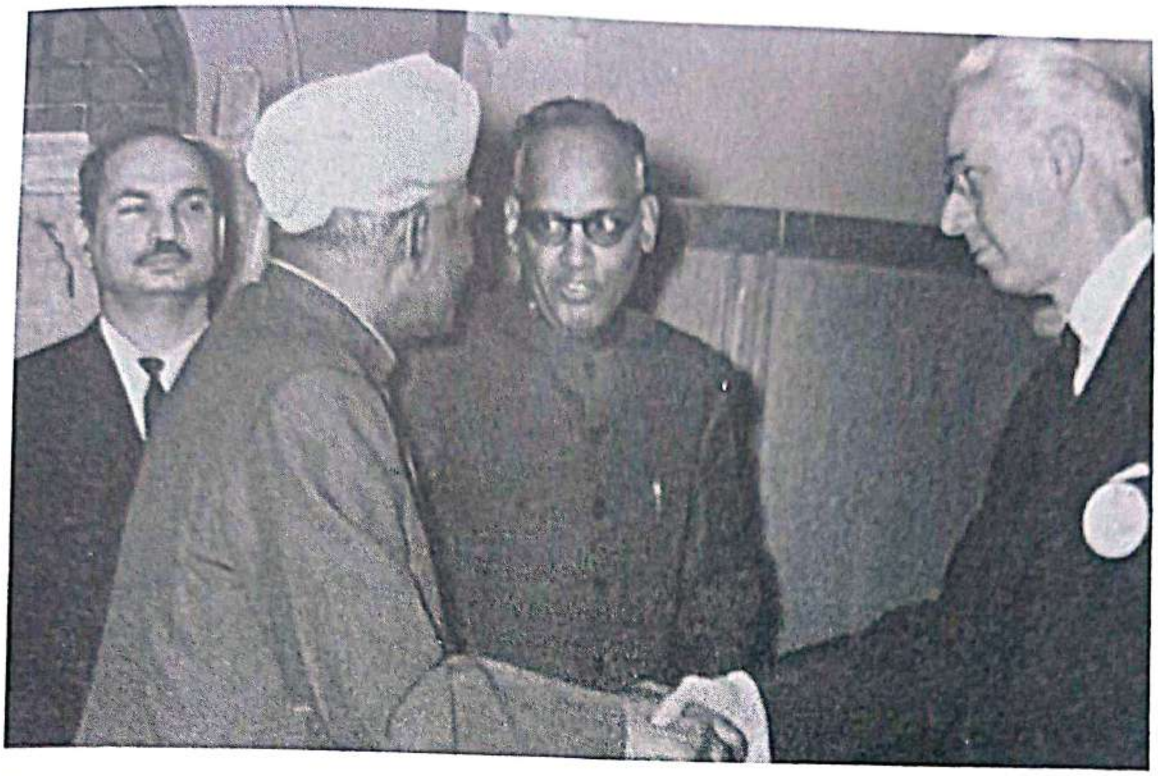


6: Alagappa Chettiar College of Technology in Guindy, Madras where all research Departments in Science of the University of Madras were located. The Physics Department headed by Ramachandran was in this building.

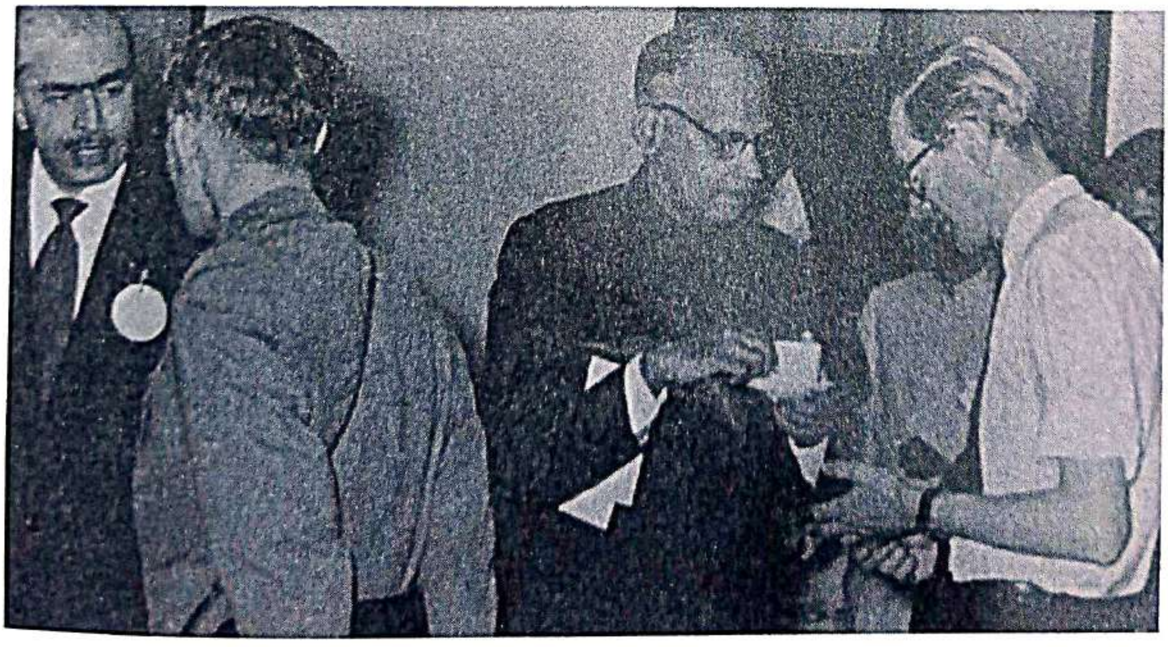


7: Professors Ramachandran and John Edsall during the latter's visit to Madras.

8: Professor Ramachandran introduces Nobel Laureate Severo Ochoa to Sir A. L. Mudaliar, the Vice Chancellor of the University of Madras. Professor Ochoa was attending the 1963 Symposium arranged by Ramachandran in Madras.



9: Professor Ramachandran introduces Professor Stanford Moore to Sir A. L. Mudaliar, the Vice Chacellor of the University of Madras. Professor Moore was attending the 1963 Symposium arranged by Ramachandran in Madras. Dr. G. Kartha is standing behind Sir Mudaliar.



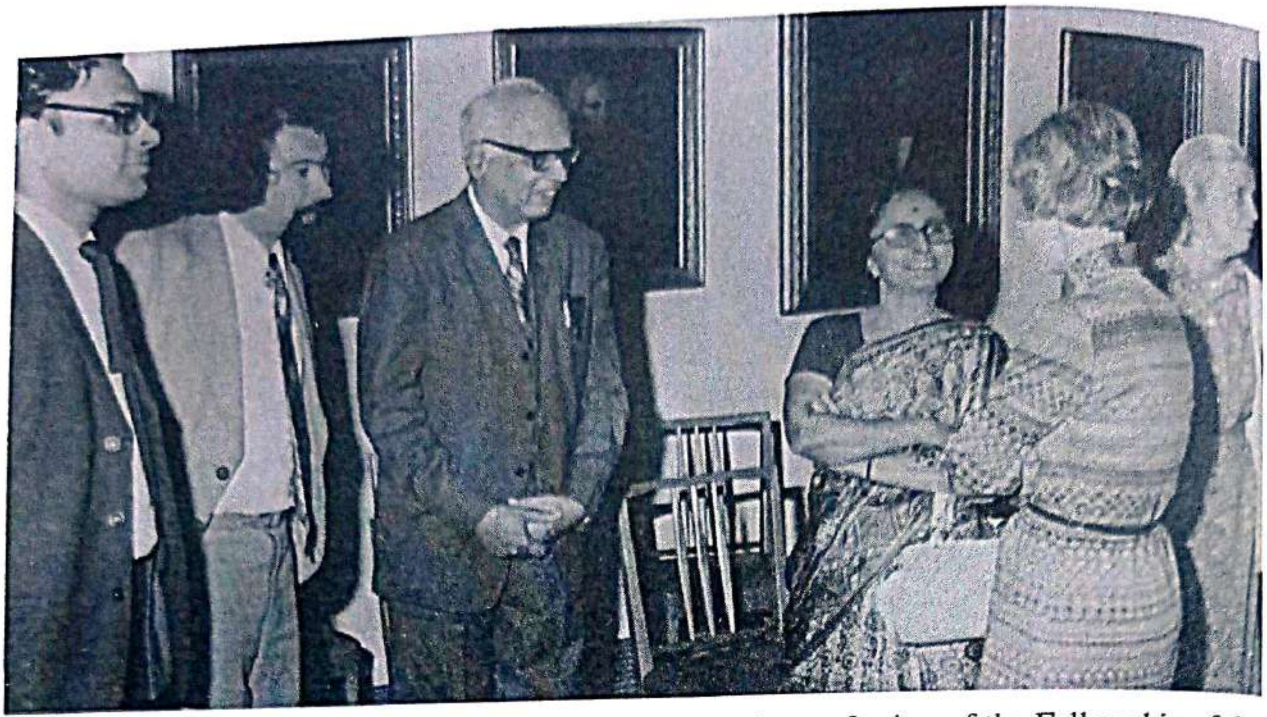
10: Professor Ramachandran is having a discussion with Nobel Laureate Maurice Wilkins during the latter's visit to attend the 1963 Symposium in Madras. Professor Wooster has his back to the camera.

11: Nobel Laureate and Professor Sir C. V. Raman (left) greets Sir A. L. Mudaliar (right) with a traditional Indian "Namasthe".

12: Professor Ramachandran and some of his students on a picnic to Mahabalipuram near Madras. Second from right is Dr. P. M. Mathews of the Theoretical Physics Department at the University of Madras. Third from the right is the author of this biography when he was Ramachandran's student. Fourth from the right is Professor Ramachandran.

13: Photo taken during a visit to Ramachandran's department by Nobel Laureate and Professor S. Chandrasekhar of the University of Chicago. Mrs. Lalitha Chandrasekhar is on the far right.

14: Professors A. J. C. Wilson, G. N. Ramachandran and S. Ramaseshan in Mahabalipuram during Professor Wilson's visit to Madras.



15: Photo taken in Burlington House in London during the conferring of the Fellowship of the Royal Society to Professor Ramachandran. Standing from left to right are: M. Vijayan, Tom Blundell, Ramachandran, Mrs. Ramachandran, and Dorothy Hodgkin (far right).

16: Professor Ramachandran with Professor Sir Alexander Todd, President of the Royal Society of London. Ramachandran was receiving the Fellowship of the Royal Society.

4. Bangalore Again–First Job in India

Ramachandran returned to India in June of 1949 and joined the Department of Physics in the Indian Institute of Science, where he had worked for his D.Sc. degree. C. V. Raman was no longer the director of the Institute. He had left and had started the Raman Research Institute, just a couple of miles away from the Indian Institute of Science. Raman was apparently so bitter with the administrators at the Indian Institute that, as the story goes, he arranged to plant several tall poplar trees inside his new campus and then said, "You see, I don't even want to see those buildings of that other Institute from my place!"

Ramachandran was appointed an assistant professor of physics in charge of the X-ray diffraction laboratory, Professor R. S. Krishnan was the chairman of the department at the time. Some very bright young men, such as Radhakrishnan, Gopinath Kartha, and Y. T. Thathachary joined his research group. His association with Gopinath Kartha turned out to be extremely productive and eventually led to one of the most significant contributions by either man in the field of molecular biology. Kartha was one of the first graduate students of Ramachandran and he determined the structure of barium chlorate mono-hydrate as part of his Ph.D. thesis. It is difficult to understand in these days of powerful computers how one could have obtained a doctorate degree for determining the structure of a small molecule like barium chlorate monohydrate. However, it should be noted that Sir Lawrence Bragg got a Nobel Prize for discovering the simple laws governing X-ray diffraction and determining the structure of sodium chloride. Kartha went on to solve the structure of collagen in Madras with Ramachandran. When Kartha went to the United States, he was mostly responsible for solving the structure of ribonuclease A. He was also (unfortunately) responsible for attracting many of Ramachandran's best students to the United States!

The X-ray diffraction laboratory set up by Ramachandran in the Institute has grown over the years. Now it contains one of the strongest research groups in the physics department. This laboratory has produced many well-known crystallographers and has been responsible for the discovery of a large number of very important structures. It must be a matter of great pride and immense satisfaction for Ramachandran to see the seed that he planted growing into such a colossal tree. In fact two decades later, Ramachandran returned to

Bangalore and started yet another laboratory that has now become the Molecular Biophysics Unit of the Indian Institute of Science. Once again X-ray diffraction is an integral part of this unit, something discussed further in later chapters.

Life in Bangalore took on a different flavor after Ramachandran returned from Cambridge. S. Ramaseshan, P. S. Narayanan, R. Vedam, Suryan, C. Radhakrishnan (C. V. Raman's son), and several other young people were at the Institute and they used to meet every Tuesday in Ramachandran's house. Mrs. Ramachandran was well known among their friends for making the best coffee and she made it for all these visitors at their meeting. The group called itself Tau Pi Chi for Tuesday Physics Club. It worked well in those days because all the students were staying on campus in dormitories. With the hiring of Ramachandran fresh from Cambridge, there was a feeling that physics research at the Institute was entering a new era, away from the classical physics of Raman and Krishnan. These meetings of the younger faculty and graduate students on Tuesday evenings was not all that popular with some senior members of the department who tried to dampen their enthusiasm. After Ramachandran left for Madras, those meetings ceased.

5. Madras and the Glorious Days

Two years after returning from Cambridge, England, a very important event took place in the life of Ramachandran. It was to have tremendous consequences not only on his own career, but also on the lives of many young scientists in India including this author.

The University of Madras, one of three premier universities in India along with Bombay and Calcutta, was set up by the British in the early 1860s. Each university consisted of several affiliated colleges with a common mission to educate undergraduates. They enjoyed a certain amount of autonomy in what they taught, and how they taught it. Each university was responsible for awarding degrees after administering common final examinations on all subjects in these affiliated colleges. Mainly they awarded bachelor's and master's degrees in the sciences and the arts, though some affiliated colleges had postgraduate programs. On rare occasions students did original research and submitted a thesis for a doctoral degree from these colleges.

The chief academic and administrative officer of the University was the vice chancellor. At that time the vice chancellor of Madras University was Dr. A. Lakshmanaswamy Mudaliar, a leading physician and a great educator. He and his twin brother, Dr. Ramaswamy Mudaliar, a lawyer and a statesman, belonged to an aristocratic family. Lakshmanaswamy Mudaliar was one of several Indians who had been knighted by the king of England. Sir A. L. Mudaliar was an individual with an outstanding vision, imagination, and foresight; he knew how to recognize and reward merit when he saw it. He also had an enormous clout with the national politicians and other academicians of the time.

Influenced by the name and fame of Sir C. V. Raman, Sir A. L. Mudaliar decided to start a postgraduate department in experimental physics at the University of Madras. He requested that Raman come to Madras as a professor and head this department. He could have anything he wanted, financially and administratively. Professor Raman was then director of his own Raman Research Institute in Bangalore, which later became a center of excellence for outstanding research in liquid crystals and astrophysics.

Raman wrote to Mudaliar that while he himself was unable to accept the offer to head the physics department, he would recommend someone with great promise, excellent scholarship, as good as he was (if not better), and who was considerably younger than himself. The person Raman recommended was none other than G. N. Ramachandran, who had just returned from England and was in the process of setting up his research at the Indian Institute of Science. Thus began an exceedingly productive career for Ramachandran in Madras and a lasting friendship founded on mutual respect and admiration between G. N. Ramachandran and Sir A. L. Mudaliar.

When Ramachandran came to Madras in October of 1952 as the first professor and head of the department of physics at the University of Madras, he was just 30 years old. It was an extraordinary appointment, especially for this highly conservative university. The story goes that a scholarly gentleman who lived in Madras heard about the arrival of the new professor and wanted to meet him. He went to Ramachandran's residence and when Mrs. Ramachandran opened the front door, he asked her if her father was at home as he wanted to meet him. She apparently replied that her father was at his home in Bombay. The embarrassed visitor had assumed that the young lady who opened the door was the new professor's daughter for he never expected that the Professor could have such a young wife. Supposedly the visitor reported this incident to a mutual friend, Mr. C. S. Iyer, father of Professor S. Chandrasekhar of Chicago University, and speculated that the lady who opened the door for him was the physics professor's wife, perhaps of a second marriage. C. S. Iyer convinced the visitor that he knew Mr. Shankara Iyer, Rajam's father, very well and he would not give his daughter for a second marriage, so the new physics professor was indeed very young and had a young wife too.

The Department of Physics at the University of Madras started with two faculty members, one in experimental physics and one in theoretical physics. The latter appointee was Alladi Ramakrishnan who had just obtained a Ph.D. from the University of Manchester in England. He came from an influential aristocratic family; his father was Sir Alladi Krishnaswamy Iyer, a famous constitutional lawyer in Madras and one of the principal architects of the Indian constitution. In fact, the Indian constitution was partly written at his house in Madras, which is now occupied by Professor Alladi Ramakrishnan.

Alladi Ramakrishnan met Sir. A. L. Mudaliar in Geneva and tried to convince him that there should be a separate department of theoretical physics in the University of Madras in addition to whatever other department Mudaliar was planning to start. However, Mudaliar decided that it was better to have just one department with a division of theoretical physics. As it turned out, Alladi was the first to join the department in April 1952. Though Ramachandran was the first to be appointed as professor of experimental physics, he actually joined six months later. Thus, in reality, Alladi Ramakrishnan was the founding member of the department.

At that time, the physics department was located in a single room in the main building of the university on the famous Marina beach in Madras. Alladi Ramakrishnan feels that if it were Cambridge or Oxford University in England, they would have preserved that room—as the original location of the physics department—as a historical site.

Six months later Ramachandran arrived as the head of the physics department. His laboratory was located at the Alagappa Chettiar College of Engineering Technology complex in Guindy, a suburb of Madras, where a large spacious room was allocated for theoretical physics. Eventually the A. C. College campus became the site of several other science departments of the University.

Ramachandran brought with him at least two people from the Indian Institute of Science—Gopinath Kartha and Y. T. Thathachary came as postdoctoral fellows. Three graduate students, M. A. Lonappan, K. S. Chandrasekharan, and S. Raman, joined the laboratory during the first year. According to Ramachandran, "Gopinath Kartha was my first and best post doc I ever had. K. S. Chandrasekharan and M. A. Lonappan joined me for doing their Ph.D. degrees; the former came from the Atomic Energy Commission and promised to continue with me even after getting his Ph.D. Lonappan found out that he would not be promoted in an Ernakulam college without a doctoral degree. P. M. Mathews joined Alladi Ramakrishnan in July of 1952, unfortunately I joined the department in September of 1952, I wish I had come in July so I could have had Mathews for my student, I feel very bad about not having Mathews as my student." These initial founding members of the physics department have gone on to make exemplary contributions in the field of X-ray crystallography and have become leaders in their own right in biophysics at other centers in India.

Within a few years, Ramachandran's laboratory acquired several X-ray generators. Students were being admitted for research leading to a doctorate degree, but it was felt that the standards and the preparation for students coming out of the affiliated colleges were rather inadequate. Therefore, it was decided that there should be an M.Sc. course as a prerequisite for anyone admitted for the doctoral program. At least in the beginning Ramachandran did not believe that separate support was necessary for courses in theoretical physics, but he allowed Alladi Ramakrishnan to go ahead and start the M.Sc. courses he wanted. Thus, concurrent lectures on X-ray crystallography and theoretical physics were planned, and students could get a master's degree in either field of study.

6. Collagen

Ramachandran continued the work on X-ray crystallography that he started at the Indian Institute of Science. An important turning point in his scientific career occurred when Professor J. D. Bernal visited Madras during late 1952 and early 1953. Bernal, a professor at the Birkbeck College in London, was one of the most respected crystallographers in England. He was regarded by many as a genius and respected as a saint. Says Ramachandran:

> I was tremendously influenced by Pauling's discovery of the alpha helix in 1951, and wanted to work on some biological problems. Even when I was a student in Raman's laboratory, two books on Raman's shelf attracted my attention and left a profound impression on me. They were *The Nature of The Chemical Bond* by Linus Pauling and *Natural and Synthetic High Polymers* by Kurt Meyer. So when Bernal visited Madras I asked him for advice. He said that he was familiar with the work in structural biology in Cambridge and London and asked me if I had read about collagen. He said that he was not at all satisfied with any model proposed for its structure at that time. The only polypeptide structures known at the time were those for the silk fiber (beta sheet) and of course the alpha helix. Cellulose was another macromolecule whose structure was also known.
>
> In fact Bernal pointed out that we could get a specimen of collagen from our neighboring Central Leather Research Institute [CLRI]. There was also the biochemistry department of the University of Madras where Professor Damodaran, head of the department, and his student L. K. Ramachandran were working on the biochemistry of fish collagen. Unfortunately, the specimen did not give a good X-ray diffraction pattern. So we asked Dr. Nayudamma, the director of the CLRI, for some kangaroo tail–tendon collagen. He got it for us from Australia."

At this point it is useful to briefly review the developments in structural molecular biology, especially as it existed during that period. One of the most important, universally accepted dogmas in molecular biology is that "structure determines function." This is true for all biological molecules, organelles, and cells. Proteins perform a variety of tasks in the cell and their structures determine their functions. Four levels of structures are defined for proteins: Primary structure refers to the linear sequence of amino acids in proteins; secondary structure defines the spatial arrangement of a small number of amino acids that are near one another in the linear sequence; tertiary structure refers to the three-dimensional arrangement of all amino acids in a protein; and finally the quaternary structure defines the spatial arrangement of subunits in proteins. X-ray crystallography has been used successfully to determine structures of small molecules. Bernal and one of his illustrious students, Dorothy Crowfoot Hodgkin, had suggested that the same technique could be used to determine the tertiary structure of proteins.

In 1951, Pauling described the alpha helix as a stable form of secondary structure in proteins. This was done long before any concrete experimental evidence was available for any protein structure. The first protein structure that clearly showed alpha-helical segments was myoglobin, whose crystal structure was determined in 1953 by John Kendrew and his coworkers in Cambridge, England. In 1953, James Watson and Francis Crick made the momentous discovery of the double-helical structure of deoxyribonucleic acid, or DNA. DNA is made up of four nitrogen- containing compounds called bases: adenine, cytosine, guanine, and thymine. Each base is connected to a backbone structure made up of a repeating sequence of a sugar and a phosphate group. An important feature of the actual structure, and perhaps the most significant contribution by Watson and Crick to molecular biology was the idea of base pairing in DNA—adenine always pairs with thymine and cytosine always with guanine. This concept revolutionized modern molecular biology.

In England and in the United States a number of distinguished crystallographers and leaders in the field were working for over two decades on structures of fibrous proteins. The most important centers of fiber research were Leeds, London, and Cambridge in England and the Massachusetts Institute of Technology (MIT) in the United States. William Astbury, famous for his work on the structure of silk and keratin fibers (hair), was a professor in Leeds and was the undisputed leader in X-ray diffraction of fibrous proteins. As Richard Dickerson writes in one of his extraordinarily informative review articles on collagen: "W. T. Astbury was a man who had the gift of seeing castles where others saw bricks."

The second group was at King's College, London, headed by Sir John Randall, who had a large number of young scientists working on various biological molecules. Among them were Maurice Wilkins and Rosalind Franklin who were working on the structure of DNA.

Then there was the nucleus of what was to become the renowned Medical Research Council Laboratory of Molecular Biology in Cambridge, spearheaded by none other than Sir Lawrence Bragg. Bragg had assembled a group of very bright young scientists including Max Perutz, John Kendrew, Francis Crick, James Watson, David Phillips, Richard Dickerson, and Alexander Rich, all of whom were deeply involved in deciphering the structures of all sorts of biological molecules. Watson and Crick had already succeeded in unraveling one of the most fundamental mysteries in molecular biology when they used X-ray diffraction to discover the structure of DNA. Crick, Cochran, and Vand had developed the theory of diffraction by helical structures, a major theoretical breakthrough in the analysis of fiber X-ray diffraction. Rich and Crick were already building models of collagen and related polypeptides.

In the United States, Richard Bear was working on collagen and other fibrous proteins at MIT in late 1940s. His diffraction photographs of collagen were some of the earliest available and formed the basis for many structures that were being proposed.

It was under these circumstances that Ramachandran and Kartha ventured into the study of collagen and within two years came up with a molecular structure that was totally innovative and contained several extremely elegant features. They were the first to propose a "triple coiled-coil" structure for collagen. Even after four decades this structure is still accepted as the correct model for collagen. In fact, when Ramachandran and Kartha published their first paper on collagen in 1954, the British scientists working on fiber structures had never heard of these two Indian scientists, much less that they were working on the structure of collagen (A. C. T. North, personal communication).

Collagen, one of the more abundant mammalian proteins, is a fibrous protein as opposed to a globular protein. It forms long fibers and is insoluble in water. Globular proteins on the other hand are smaller in size and are shaped like a sphere or ellipsoid. Collagen is a major component of bone, tendon, cartilage, and teeth and gives structural integrity to the animal. X-ray crystallography is the only method that is suitable for determining complete molecular structures of proteins. Ramachandran was an X-ray crystallographer and was more than adequately trained to undertake the determination of collagen structure. Professor Bernal had drawn his attention to the many different unacceptable models reported in the literature by such pioneers in this field as Astbury, Pauling, Corey, Randall, and Crick.

All proteins are made up of amino acids linked together by what is known as a peptide bond. An amino acid has a central carbon atom, known as an alpha carbon atom, connected to four different chemical groups. Three of the four groups are identical in all amino acids: (1) a hydrogen group (— H); (2) an amino group (— NH_3^+); and (3) a carboxylic acid group (— COO^-). The fourth group, called the side chain, contains different sets of atoms in different amino acids. Some amino acids are well known as supplementary nutritional components in our food. All naturally occurring proteins in this world are made up of twenty different kinds of amino acids. Several hundred amino acids of the twenty different kinds are linked together to form a protein, also called a polypeptide chain. The sequence of the twenty amino acids in

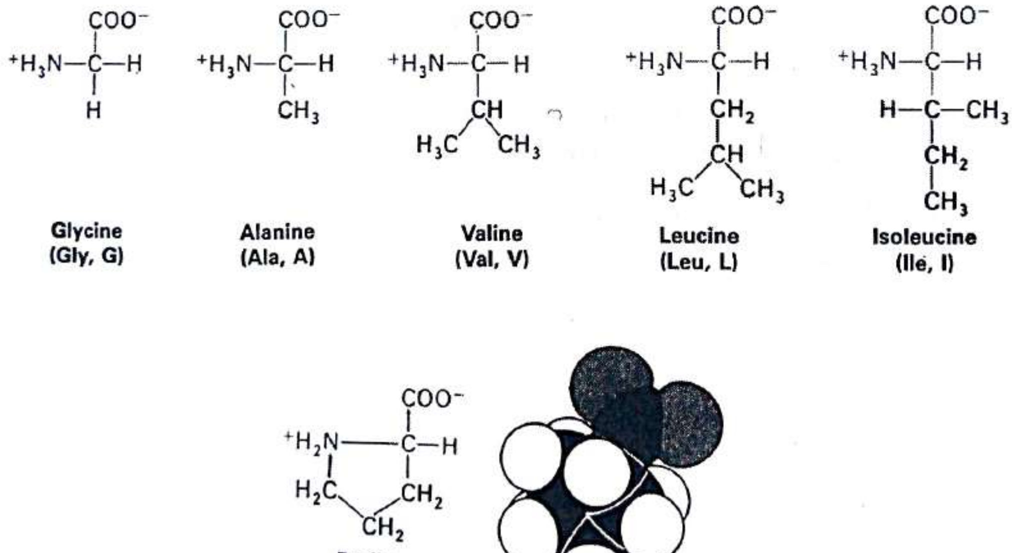
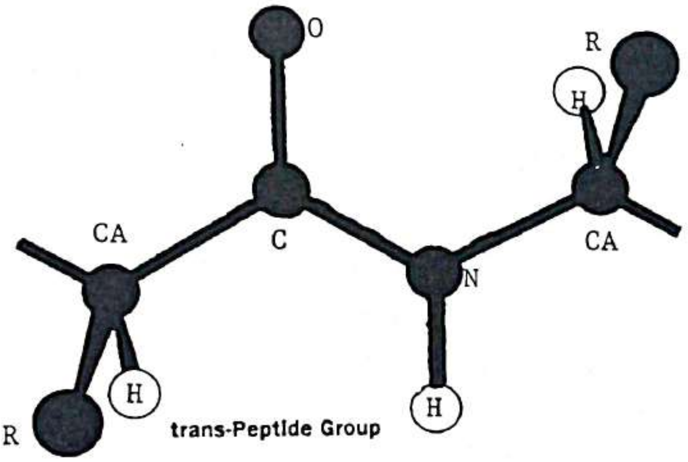


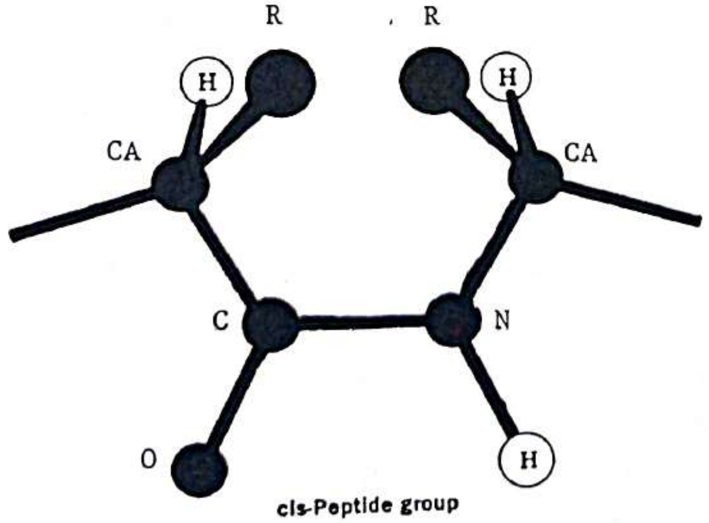
Figure 1: Examples of structures of amino acids found in proteins. A central carbon atom, called the alpha carbon is attached to four groups of atoms, three of which are common to all amino acids. They are H, COO^- and NH_3^+. The fourth group of atoms called the side chain is different in different amino acids. Collagen has an unusually large amount of proline and a modified amino acid called hydroxyproline. In proline the last carbon atom in the side chain is connected by a covalent bond to the nitrogen of the amino group. The hydroxyl group in hydroxyproline is attached to the second carbon atom in the side chain.

any protein is determined by the sequence of four different kinds of nucleotides in the gene, which is a molecule of deoxyribonucleic acid.

Collagen has some unusual chemical properties; it is a protein made up of three separate polypeptide chains held together by covalent and non-covalent interactions. These chains form the long insoluble fibers of collagen. Each chain has a special amino acid composition. Nearly one-third of all amino acid residues in collagen is glycine, the smallest of all amino acids found in proteins. The side chain of glycine consists of a single hydrogen atom. All remaining nineteen amino acids found in proteins have more atoms in their side chains. The second most abundant amino acid in collagen is called proline and a modified form of proline called hydroxyproline. In fact, nearly a quarter of all amino acids in the three chains of collagen consists of proline and hydroxyproline. Proline itself



trans-Peptide Group



cis-Peptide group

Figure 2: Trans and cis peptide groups. The bond connecting the Carbon and Nitrogen atom is called the peptide bond. CA stands for the C alpha atom of an amino acid. In trans peptides the oxygen attached to the carbon and the hydrogen attached to the nitrogen are on opposite sides of the C-N bond. In cis peptides they are both on the same side.

is a unique amino acid because, unlike all other amino acids, the last carbon atom in the side chain of proline forms a chemical bond with the nitrogen atom of the amino group that is attached to the alpha carbon atom, forming a ring structure. This makes proline structurally very rigid.

No other naturally occurring protein has such a unique amino acid composition. All investigators working on the structure of collagen knew that its unique amino acid composition must somehow influence its three-dimensional structure, which in turn determines its function, namely to provide structural integrity to vertebrates.

In the cell the gene coding for collagen is transcribed into a messenger ribonucleic acid (RNA) which is translated into a protein using a universal genetic code. The protein-synthesizing machinery of the cell incorporates proline in appropriate locations in the growing collagen chain. After the polypeptide chain is synthesized, an enzyme called proline hydroxylase attaches a hydroxyl (— OH) group to a specific carbon atom of some selected prolines converting them to hydroxyprolines. This process is known as "posttranslational modification." The proline hydroxylase enzyme requires vitamin C or ascorbic acid for its proper function. Absence of vitamin C in our diet results in a malfunction of the proline hydroxylase enzyme producing an inadequate formation of hydroxyproline and defective collagen. This is the cause of the disease known as scurvy that affected many sailors in olden times, who did not consume fresh fruits or vegetables while at sea and so did not receive an adequate supply of the required vitamin C.

A second experimental observation was based on infrared spectroscopy of collagen fibers. The conclusion was that collagen structure had absolutely no *cis* peptide bonds, instead all are *trans* peptide bonds. A peptide bond is a chemical bond formed when two amino acids combine to form a dipeptide. A dipeptide combines with a third amino acid via a peptide bond to form a tripeptide, and so on. The atoms forming the peptide bond are the carbon of the carboxylate group of the first amino acid and the nitrogen of the amino group of the second amino acid. In a *trans* peptide bond, an oxygen atom attached to the carbon atom and the hydrogen attached to the nitrogen atom are on opposite sides of the bond. On the other hand in a *cis* peptide bond the oxygen and the hydrogen atoms are on the same side of the peptide bond.

Richard Dickerson has very elegantly and exhaustively reviewed the history of structure analysis for collagen in the second volume of *Proteins*, edited by Hans Neurath and published in 1964 by the

Academic Press. According to Dickerson, "There have been more work and more trial structures connected with collagen than with any other fibrous protein, and to trace the evolution of the structure of collagen is to trace the evolution of fibrous protein crystallography in miniature."

To trace the evolution of fibrous protein crystallography it is necessary to understand some basic principles of X-ray structure determination. Some molecules form single crystals and some molecules form long fibers. Sodium chloride, sucrose, and copper sulfate are examples of small molecules that form single crystals. Even large protein molecules like myoglobin and hemoglobin can be manipulated to form single crystals. Hair is made up of a protein that forms long fibers like collagen or DNA. There is a fundamental difference in the methods used to determine structures of single crystals and fibers.

When single crystals or fibers are placed in a powerful beam of X-rays, they give rise to what is known as a diffraction pattern, which is characteristic of the structure of the molecule present in the crystal or in the fiber. The diffraction pattern is usually recorded on an X-ray film. When the film is developed, a single crystal diffraction pattern will show a number of dark spots. These are called "reflections" because they may be interpreted as arising from reflection of X-rays from planes of atoms in the crystal.

Molecules are arranged in a highly ordered three-dimensional lattice in single crystals. On the contrary, in fiber specimens, the molecules may all be arranged parallel to one another on individual bundles, but the orientation of the bundles with respect to one another may not be the same throughout the specimen. As a result fiber specimens give diffuse or smeared reflections in their diffraction pattern, as opposed to extremely sharp reflections obtained from single crystals. This has serious consequences for the methods used and the results generated.

The spatial distribution or the distance between the reflections in a diffraction pattern depends upon the spatial arrangement of molecules in the lattice of the crystal or fiber. However, the actual structure of the molecule or the exact three-dimensional arrangement of all atoms in the molecule of the compound determines the distribution of the intensities in the various reflections of the diffraction pattern.

A single crystal specimen usually gives rise to many more reflections in its diffraction pattern than a fiber specimen. The intensities of all such reflections are used to calculate a distribution of electron density in the molecule of the crystal. Since electron density has large values only where atoms are present, the positions of peaks in the electron density map will correspond to positions of atoms in the three-dimensional structure of the molecule. X-ray diffraction analysis of single crystals is the only biophysical method that is capable of revealing the three-dimensional structures of molecules.

In the case of a fiber specimen, such a calculation is not possible because of the insufficient number of reflections in its diffraction pattern, and different strategy is used to determine their structure. Most fibrous proteins form helical structures. The spatial arrangement of reflections in a fiber diffraction pattern may be used to calculate various parameters of the helical structure, such as its radius, pitch, and the vertical height between repeating units of the helix. These parameters are used to build a model of the molecule of the fiber. The spatial coordinates of all atoms in the model are then measured. The structure of a fibrous protein derived in this fashion is less unique and less accurate than that of a crystalline protein because the model is not directly based on an actual distribution of the electron density.

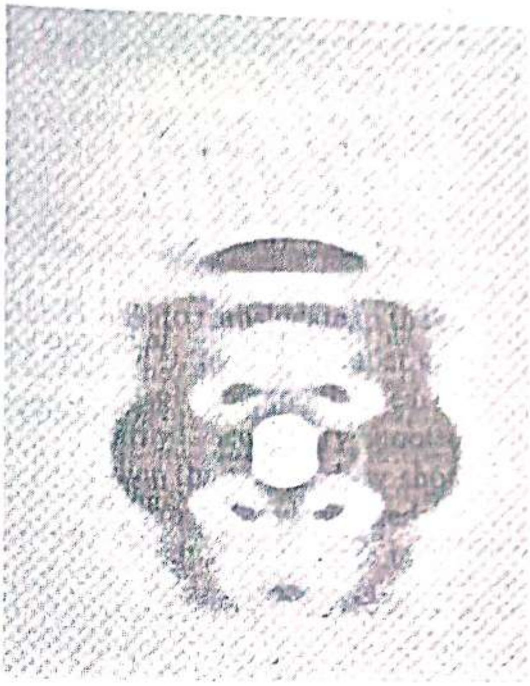
Once the structure of a molecule is determined, it is possible to use the positional coordinates of all atoms in the structure and calculate the intensities of all reflections in its diffraction pattern. The calculated intensities are compared with those measured experimentally. If there is good agreement between the two, it may be concluded that the proposed three-dimensional model for the structure is most probably correct.

Collagen from any source exhibits an extensive and well- developed wide-angle X-ray diffraction pattern, and most forms of collagen show a characteristic well-defined small-angle pattern as well. The former can be used to determine the structure of the molecule at the atomic and molecular level and the latter has been used along with electron microscopic data to discover how the molecules aggregate into fibers.

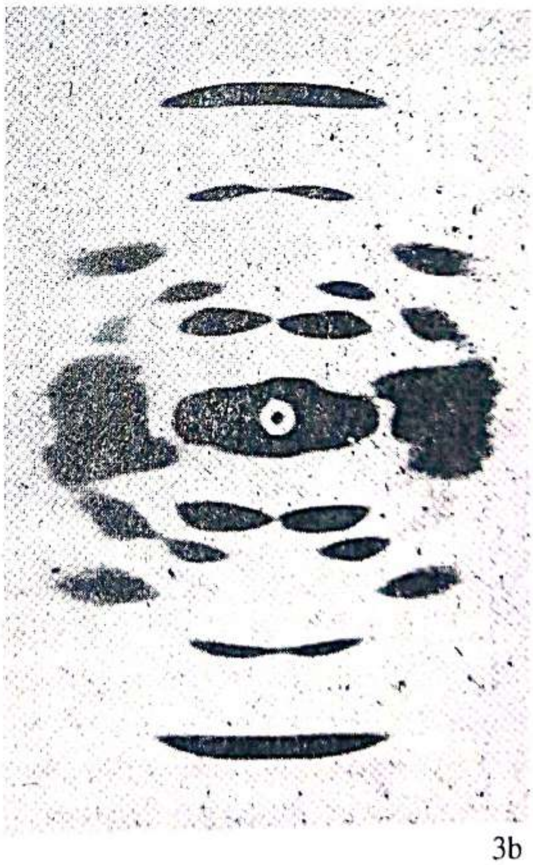
Ramachandran and his student Gopalakrishna Ambady, in a paper published in *Current Science*, presented the main features of the wide-angle X-ray diffraction pattern of collagen. There were several significant features. A strong meridional arc at 2.9Å; layer lines at 9.5 and 4Å, each with a pair of off-meridional spots; a diffuse cloudy spot on the equator around 4.5Å (arising from an aggregate of several diffuse spots); clouds of optical density above and below this equatorial group; a radial component at about 4.5Å and extending up to the 4.0Å layer line; and a very dense moisture sensitive equatorial reflection at about 11Å.

Analysis of the sequence of peptide fragments of collagen had shown that tripeptides of the type Gly.Pro.Hypro and Gly(Pro or Hypro). Gly were very common. In general glycine was evenly distributed and was usually clustered in certain peptide fragments, whereas proline and hydroxyproline were unevenly distributed. The conclusion of such studies was that every third residue in collagen was probably glycine, but that any model would have to accommodate sequences of the type .Gly.Pro.R. and .Gly.Pro.Hypro.

The first paper on collagen by Ramachandran and Kartha appeared in the August 1954 issue of *Nature*, the highly reputable London-based journal. The authors submitted this paper less than two years after they started their research on collagen, and the editors of the journal published the article five months after they received it. The proposed structure consisted of three polypeptide chains arranged in the form of cylindrical rods in a hexagonal array. The amino acid residues in each polypeptide chain formed helices of pitch 9.5Å, and contained three residues per turn. The amino acids showed what is called a 3_1



3a



3b

Figure 3a: X-ray diffraction pattern from collagen. The pattern is taken with the collagen fiber mounted at an angle to the incident x-ray beam.

Figure 3b: Optical diffraction pattern produced by the triple helical collagen structure. This is produced by shining visible light through a two-dimensional mask in which tiny holes are punched at atomic positions of a projection of the collagen structure.

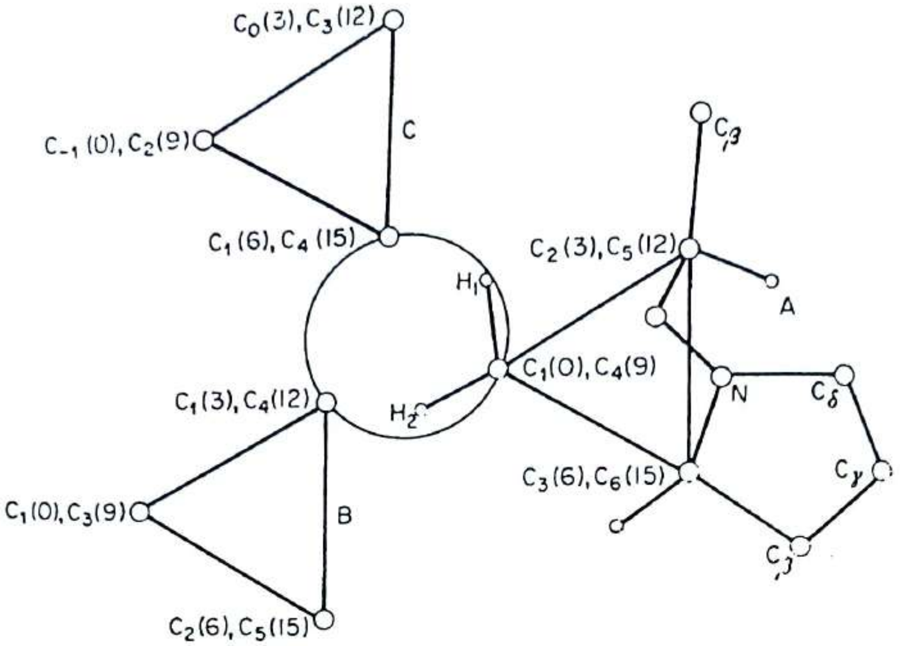


Figure 4: Schematic diagram of the prototype collagen structure consisting of three helical chains standing side by side. The α-carbon atoms are indicated by circles and the peptide units by straight lines joining them The heights of the atoms in Ångstroms along the helical axis are indicated in brackets.

symmetry, which occurs when an object repeats itself after a rotation of 120 degrees followed by a translation of one-third the unit repeat distance which in this case is about 3.17Å parallel to the rotation axis. The three chains forming the cylindrical rods were held together by hydrogen bonds. Two of the three NH groups in each turn of a chain were linked by hydrogen bonds to an atom of oxygen in each of the other two chains, the NH...O distance was 2.8Å. The third NH group pointed outward from the cylinder and this nitrogen atom formed part of a proline ring. This helix was completely different from the alpha helix discovered by Pauling and Corey, in which the hydrogen bonds were formed within the helical polypeptide chain. Ramachandran and Kartha's paper gave the first clue to the scientists in the collagen field that two unknown Indian scientists were working on the structure of collagen. Surprisingly, neither author had ever presented their results at any conference on collagen, in or outside India.

Their structure also differed from a three-chain model for collagen proposed by Pauling and Corey (*PNAS*, 37, 272, 1951). They were the first to propose structures with helical cylinders packed in a hexagonal lattice. They assumed that two out of every three residues formed *cis* peptide bonds and each chain would have nine *cis-cis-trans* triplets. As in the Ramachandran structure, the hydrogen bonds were between the chains. The model exhibited good bond lengths and angles. Two out of every three possible hydrogen bonds were formed. Defects in this model however were numerous, as for example the presence of a large number of *cis peptide bonds*. Pauling's collagen structure was wrong; nevertheless, it marked an important advance in being based firmly on helix diffraction theory and in giving the best agreement yet between the observed diffraction pattern and that calculated from the model.

In 1954, Francis Crick (*J. Chem. Phys.*, 22, 347) set out to satisfy the criteria of the helical structure and proposed a left-handed two-chain helix. Each chain had two residues per 2.9Å, one of the amide planes was perpendicular to the helix axis and the other one was parallel. Each perpendicular amide was hydrogen bonded to its corresponding member across the two-fold axis. This was one of the first structures to give good qualitative agreement with the entire diffraction pattern. The optical transform of this model compared well with the collagen diffraction pattern. But like all its predecessors this structure too had crippling faults:

1. The quantitative agreement between the diffraction pattern calculated using the structure and that observed experimentally was very poor.
2. All amides were in the *cis* configuration, whereas infrared studies suggested that only the *trans* configuration was present.
3. There were rather close interatomic contacts.

Thus two models for collagen appeared in 1954: Ramachandran and Kartha's model consisted of cylindrical "ropes", each rope containing *three* separate helical chains, stacked in a hexagonal array and connected by hydrogen bonds. The second model proposed by Francis Crick consisted of a two-chain left-handed helix in which peptides were in a *cis* configuration.

In the mean time, Gopalakrishna Ambady, a graduate student in Ramachandran's laboratory obtained very clear diffraction patterns from stretched collagen fibers in which the specimen was placed at an angle to the incident X-ray beam instead of being perpendicular. The new diffraction photograph taken by Ambady confirmed an earlier observation by the King's College group that a reflection at 2.86Å spacing was indeed along the meridian. A reflection on the meridian measures the periodicity along the axis of the fiber. Ramachandran and Kartha's model however failed to explain this reflection, which was interpreted by them as due to an overlap of two non-meridional reflections on either side of the meridian.

In view of the above, Ramachandran and Kartha had to revise their first structure. They were influenced by the fact that the structure was unmistakably helical and contained only trans residues. The helix in the first structure contained 3 residues per turn, while Ambady's X-ray data indicated that the helix should contain 3.33 residues per turn. Fractional number of residues

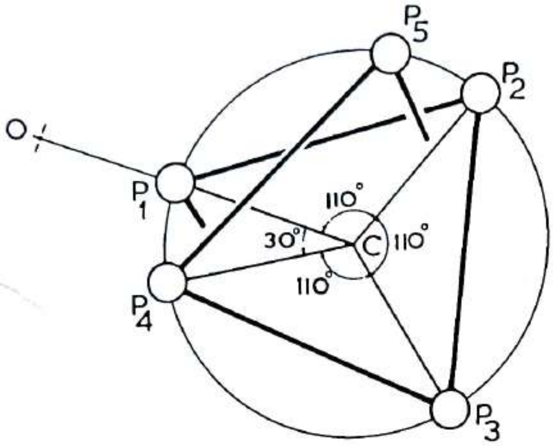


Figure 5: A single chain having approximately 3¹/3 residues per turn.

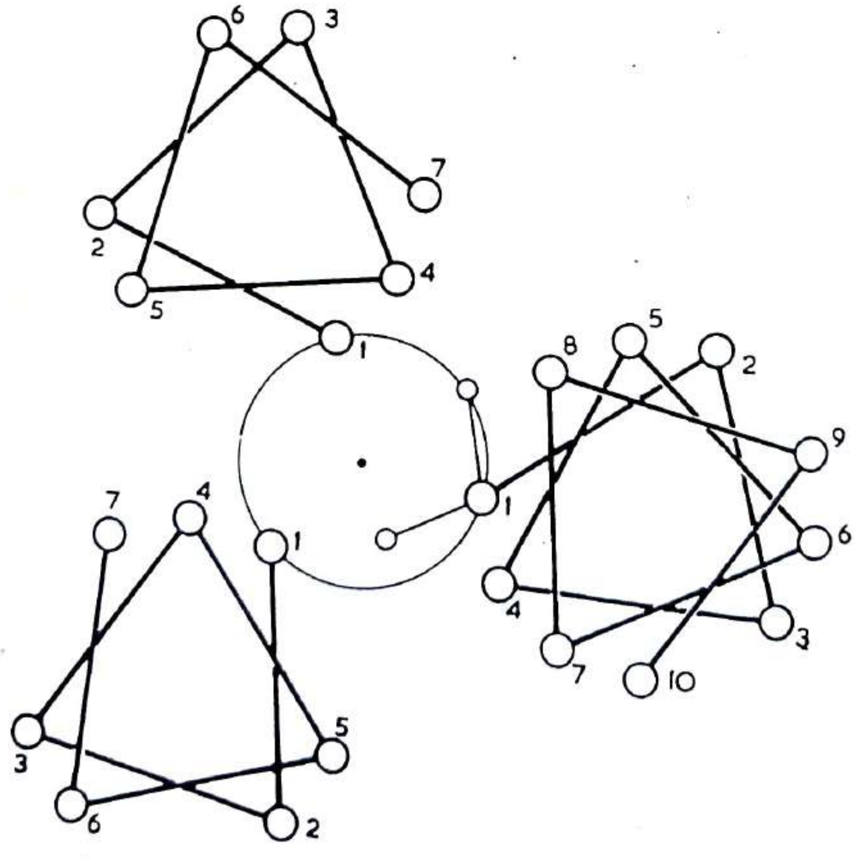


Figure 6: Three such chains put side by side. Note that the α-carbon atoms 4, 7, etc., come progressively out of the inside of the triple helix.

in one turn in the present case was the same as 10 residues in 3 turns.

Ramachandran and Kartha published a second paper incorporating a revision of their first structure in the September 1955 issue of *Nature*, nearly four months after it was received by the journal's editors. The implication of this delay in publication will become clearer later in this chapter.

This turned out to be a seminal paper in the field of collagen structure, because for the first time the authors presented a totally new concept for the structure of collagen. They introduced the idea of a "coiled coil"; a motif that has remained unchallenged for the past four decades. The structure explained almost all the experimental observations on collagen.

This revised structure contains three polypeptide chains, each chain arranged in the form of a helix. The three chains, instead of being arranged with their axes parallel to the fiber axis as in their first structure, are now allowed to form a second helix. The resulting architecture is described as a "coiled coil." Thus every third alpha carbon atom is placed on the surface of a cylinder of radius 1Å, the successive ones being displaced by 8.58Å along the axis of the cylinder and rotated through an angle of 36 degrees about that axis. The coiled coil repeats itself after thirty residues with a repeat distance of 85.8Å along the fiber axis. The three chains are symmetrically disposed with respect to one another.

Thus each collagen chain may be described as consisting of a minor

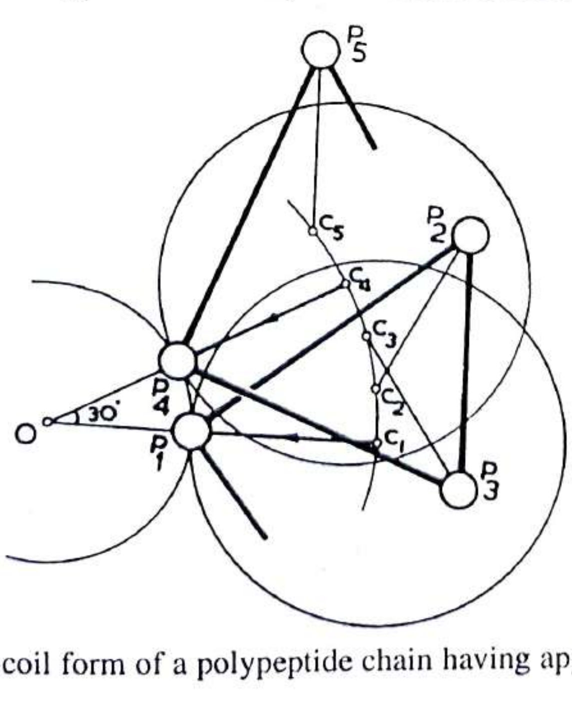


Figure 7: Coiled-coil form of a polypeptide chain having approximately 3 1/3 residues per turn.

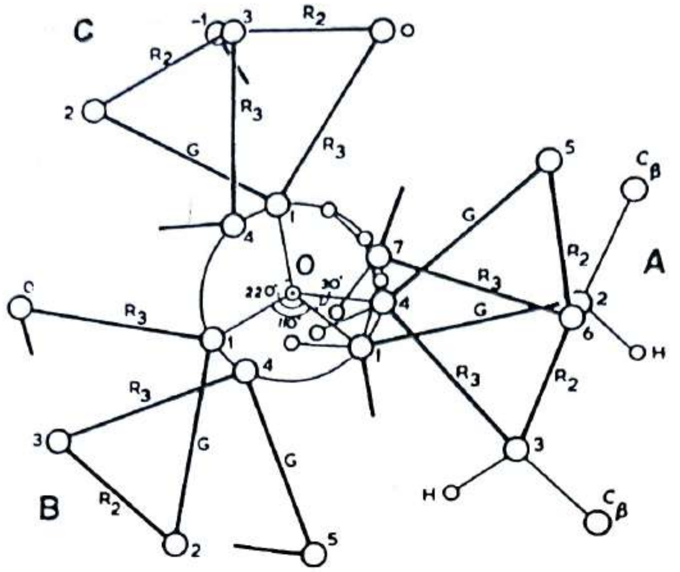


Figure 8: Three such coiled-coil chains put side by side. Note that the α-carbon atoms 1, 4, 7, etc., all occur on the inside of the triple chain. This scheme is the basis of the collagen triple-helical structure.

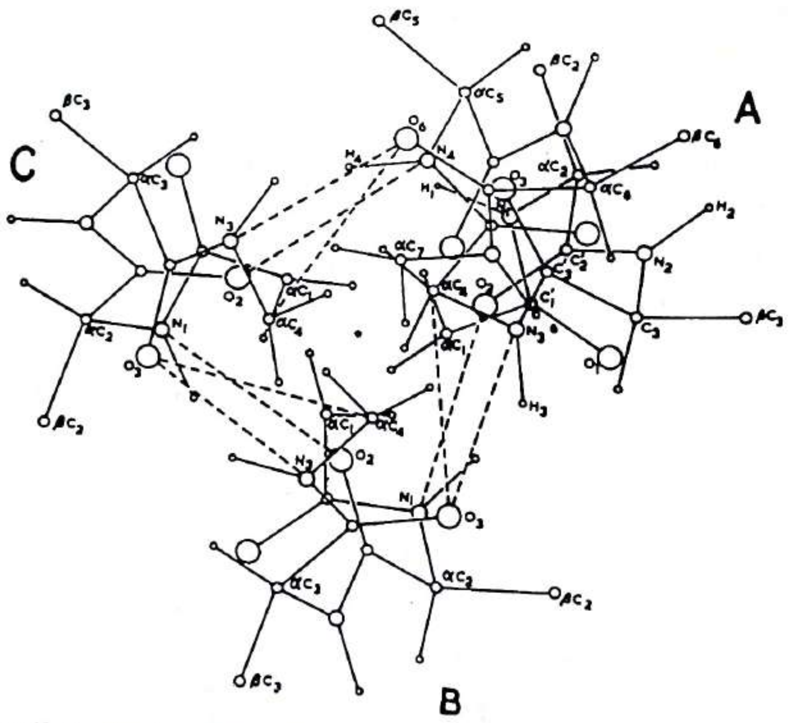


Figure 9: The detailed atomic arrangement in the coiled-coil triple chain structure of collagen. Note the occurrence of two NH...O and one CH...O hydrogen bonds for every three residues.

helix having ten residues in three turns and a vertical rise of 2.91Å per residue along the fiber axis. This is wound to form a major helix of radius 2.5Å, with thirty residues per turn. The major helix is wound in a direction opposite to that of the minor helix, which is like a left-handed screw if all the residues are of the L-type*. Thus, while the thirty residues make nine turns in the coordinate system of the minor helix, they make ten turns in the coordinate system of the major helix; this ensures that every third residue is similarly situated with respect to the fiber axis.

The coiled-coil structure makes two types of interchain N – H . . . O hydrogen bonds, repeated uniformly by the screw axis symmetry. The N . . . O distance is about 2.9Å and the angle between NH and N . . . O directions is about 30 degrees. (This angle would be zero if N, H, and O are collinear.)

Two of every three NH groups in one turn of a major helix are hydrogen bonded to an oxygen atom of a CO group in a neighboring helix, but the two oxygen atoms to which they are linked are contributed by different amino acids. Thus, of every three carbonyl oxygens only one does not take part in internal hydrogen bonding in the triple chain cylindrical rods. This oxygen atom points outward from the rod and plays an important part in cross-linking of the rods by side chains. Every third residue must be a glycine and a maximum of one third of the residues may be proline or hydroxyproline.

One major consequence of this model is that the 2.8Å reflection would be meridional as indicated by Ambady's diffraction pattern and the only other meridional reflections are from its higher orders. The intensity distribution along the equator and the repetitive unit along the fiber axis agree well with the observations of Ramachandran and Ambady. The oxygen atom of hydroxyproline is nearly as far away from the axis of the cylinder as is possible. Thus, internal hydrogen bonding of the OH group in hydroxyproline is ruled out. These groups take part in linking the cylindrical rods with one another; the hydroxyproline OH group in one rod is nearly at the same level as the exposed non hydrogen-bonded-carbonyl oxygen of the neighboring rod so that they could be readily linked by an O– H . . . O hydrogen bond.

"If the coiled coils described above are simply put together in a hexagonal array, then only some of the hydroxyproline OH groups are bonded to carbonyl oxygens of neighboring rods. However, a very slight change in the pitch of the major helix is sufficient to make the

---

*The four groups on the alpha carbon atom of an amino acid are arranged in a specific order for an L amino acid. An alternate arrangement produces a D amino acid. L and D amino acids are mirror images of one another. All naturally occurring proteins in this world are made up of only L amino acids, although D amino acids are found in various smaller biological polypeptides and bacterial cell walls.

number of hydroxyproline-carbonyl hydrogen bonds a maximum. Instead of a rotation angle of 36 degrees per three residues about the axis of the major helix, the angle must be reduced to 35 degrees. This immediately introduces a 6_1 symmetry for the major helix which repeats after 216 residues (618Å), highly suggestive of the 640Å spacing found in the small angle X-ray pattern and the electron micrographs of collagen."

The above paper by Ramachandran and Kartha raised several eyebrows in England. Basically the structure was sound and explained most of the experimental results. Several pioneering investigators of the time must have wondered how they missed such a logical concept as a coiled coil structure and must have been dismayed at not being the first to propose such a motif for the structure for collagen. They were still toying with *cis* and *trans* peptides and two helices like in the DNA structure. Without doubt this single idea of a coiled-coil led to a major triumph in the elucidation of the correct structure of collagen. Ironically, it was also the beginning of a minor controversy and a major disappointment for the Madras group in general and Ramachandran in particular.

Alexander Rich and Francis Crick published their version of the structure of collagen in the November 1955 issue of *Nature*, within two months of the publication of Ramachandran and Kartha's paper. They stated in very forthright language that the actual structure proposed by Ramachandran and Kartha "was wrong." Interestingly this paper appeared in print within a month after it was received by the editors of *Nature*, while it took the same editors almost four long months to publish Ramachandran and Kartha's paper that contained the original coiled-coil structure of collagen.

To quote from the Rich and Crick paper:

> Very recently Ramachandran and Kartha have made an important contribution by proposing a coiled-coil structure for collagen. We believe this idea to be basically correct but the actual structure suggested by them to be wrong.
> Their structure consists of three polypeptide chains, each having approximately three-fold screw axis. In addition the chains slowly wind around each other to form a coiled coil, thus reproducing the observed non-integer screw axis. The major helix is right-handed, the minor one left-handed.

> Each chain is held to its neighbors by two sets of systematic hydrogen bonds. The allowed sequence of residues is -G-R-P-G-R-P- etc., where G implies glycine only, R implies any residue except proline or hydroxyproline and P implies any residue, but usually proline or hydroxyproline.
> We believe this structure to be wrong for two reasons:
> (1) It is stereochemically unsatisfactory. In particular there is a very short Cα—Cα contact of 3.3Å (normally 3.6 to 4A) and an extremely short Cα—O contact of 2.6Å (nor mally 3.2 to 3.5A). In addition, the hydrogen bond angles are on the outside limit of the values usually found.
> (2) It is not compatible with recent work on the amino acid sequence which shows that gly-pro-hypro- is a common sequence in collagen.

In the same paper Rich and Crick proposed two alternate models for collagen, which they designated as structure I and structure II. Both have a right-handed major helix and a left-handed minor helix, as in Ramachandran and Kartha's structure. There is only one set of systematic hydrogen bonds linking neighboring chains. In structure I the NH group points counterclockwise when viewed from the carboxyl ends of the chains and in structure II the NH group points clockwise.

Again to quote Rich and Crick:

> These two structures are thus similar to that of Ramachandran and Kartha in being three chain coiled-coil structures; but they differ in having only one set of systematic hydrogen bonds instead of two. Moreover they are both stereochemically completely satisfactory.

They conclude that (1) no structure with two systematic sets of hydrogen bonds is stereochemically possible; and (2) no other structure with one systematic set of hydrogen bonds is stereochemically satisfactory except the two described by them. Neither were they able to invoke additional hydrogen bonds in structures I and II in a convincing manner.

When the results presented in a journal article are disputed by another group of authors in a manuscript submitted to the same journal, especially within a period of six or seven weeks, it is customary for the editors to invite the authors of the first paper to answer the criticisms and publish their response simultaneously with the second paper, even when the claim made in the second paper was very forthright. It is not clear if the editors of *Nature* did any such thing. The authors of the second paper were probably in a rush to publish their results and just could not wait to give a chance for the first authors to answer to their criticisms.

From all reasonable scientific standards the tone of Rich and Crick's paper describing the two-bonded structure to be "wrong" was clearly unfair, though the structure may have required modifications. The major difference between the two groups is in the number of hydrogen bonds and some short distances between non-bonded atoms. There was absolutely no direct experimental evidence at the time for the actual number of hydrogen bonds in the collagen structure.

Interestingly Alex Rich and Francis Crick wrote a detailed letter to Ramachandran on 1 November 1955, even before their own collagen paper appeared in *Nature*. The tone of that letter was much less critical than their paper which would appear just eleven days later. Rich and Crick write in that letter:

> . . . However we feel that your type of structure is on the right lines, and that the collagen problem has changed completely as the result of your work.
>
> We also feel that perhaps in your model building you are being too rigid in insisting on exact equivalence, and especially on exact coiled-coiling, especially as there is only one set of systematic hydrogen bonds to restrain the structure. . .

In 1955, even before the Rich and Crick paper appeared in *Nature*, Ramachandran and Kartha published a detailed paper in the *Proceedings of the Indian Academy of Sciences* (Vol. A42, 215, 1955). Obviously, this was done to avoid the kind of delay that they were experiencing with publishing in *Nature* and to hasten the release of the fine details of their new structure. Ramachandran and Kartha were indeed aware of the short carbon-oxygen distance, mentioned by Rich and Crick, explaining it as follows:

> The last (2.65Å between Carbon 1 and an oxygen) is considerably smaller than the carbon-oxygen van der Waals

> contact distance. On the other hand, if the radius of the major helix is made larger, then the NH...O hydrogen bond lengths were increased too much, although the carbon-oxygen distance was satisfactory. If one of the hydrogen bonds is made short, while the other is comparatively long and not at the correct angle, then it is possible to avoid short carbon-oxygen distances; but this arrangement was not considered satisfactory.

In the same paper Ramachandran and Kartha also addressed the second objection of Rich and Crick, namely that their structure could not accommodate the .Gly.Pro.Hypro. sequence. Once again to quote Ramachandran and Kartha:

> It had been assumed in the earlier model that the sequence of the residues was of the type -G-R-P-G- (G for Glycine, P for Proline and R for any other residue). The five-membered ring of proline or hydroxyproline residue could be attached to either the C2 or the C3 carbon (second or third residue). However C3 will be favored as the corresponding NH group is not hydrogen-bonded. The choice of the location of proline or hydroxyproline residues as well as the distribution of other residues cannot be determined from a study of the backbone of a protofibril, but rather by a discussion of their cross-linkages. The hydroxyl group of a hypro residue will be in the right position to form a hydrogen bond with the carbonyl oxygen O1 of the neighboring rod, if it occurs as residue R3. On the other hand a proline residue occurring in this position serves no such purpose. Consequently the proline may occur in position R2.

Ramachandran alone published yet another paper on the structure of collagen in *Nature* in April 1956, answering some of the criticisms in the Rich and Crick paper of 1955. Ramachandran writes:

> Rich and Crick have criticized the revised structure proposed from this laboratory, on considerations of stereochemistry and amino acid sequence. Both these difficulties were known to us and were in fact considered in a paper discussing this

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> structure in detail*. It was found impossible to avoid short contacts if two good interchain hydrogen bonds were to be formed for every three residues. Consequently, models were built up which were stereochemically more satisfactory. It was then found, as Rich and Crick have found, that only one hydrogen bond can be formed for every three residues in each chain of the triple chain. However two configurations are possible, both of which are quite satisfactory so far as the backbone of the structure is concerned. The two structures may be called the plus and the minus structures, since they could be obtained from the one described earlier by rotating the minor helices about their own axes through a positive and negative angle. These two possibilities are respectively similar to the structure I and structure II of Rich and Crick and the anticlockwise and clockwise structures of Cowan, McGavin, and North . . .
>
> Both Rich and Crick and Cowan et al. have favored the other possibility, namely the configuration analogous to our plus structure. However the minus structure appears to be more probable for the following reasons.

Ramachandran lists three reasons for the above conclusion, arguing that "there seems to be no reason why the structure should be based on an exact coiled coil, as was assumed in our studies. The X-ray pattern only demands that every third residue must occur on a simple helix of pitch 85.8Å, with thirty residues per turn, in each of the three chains. If only this condition is put in, then almost straight hydrogen bonds can be formed in the minus structure, and yet having no short van der Waals contacts. Although there are thus various points in favor of the minus structure, a second set of hydrogen bonds cannot be formed and a number of imino-hydrogens are systematically not hydrogen-bonded. This is not really satisfactory. It is possible, however, for those hydrogens to be bonded to carbonyl oxygen in another chain of the same triple chain through a water molecule. It is probable that water exists in such a firmly bound form in collagen, but a careful study is required of this question."

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*Ramachandran was referring to the detailed paper that he published with Kartha in the1955 *Proceedings of the Indian Academy of Sciences*.

7. The Controversy

Much has been written on the discovery of collagen's structure and on some of the controversy that followed. The most important fact remains the monumental success achieved by two young Indian scientists, Ramachandran and Kartha, neither of whom had any prior experience or exposure in the field of structural molecular biology—one of them had just started a new physics department, and the other had only just obtained his physics doctorate. In addition they were located thousands of miles away from England, where all the excitement in the field was taking place.

A distinct feature of collagen is its high glycine, proline, and hydroxyproline content. The structures of synthetic polypeptides containing glycine, proline or hydroxyproline might therefore be expected to bear similarities to the collagen structure. This line of reasoning led to the convergence on the triple chain coiled-coil model by two other groups besides Ramachandran's, whose paper was the first to appear in *Nature* (received on 3 June 1955 and published on 24 September 1955, three and a half months later). The other groups were (1) Rich and Crick from Cambridge (received 10 October 1955 and published 12 November 1955, four weeks later), whose collagen model was derived from their work on polyglycine; and (2) the King's College group of Randall, Cowan, North, and McGavin (received 10 November 1955 and published 3 December 1955, three weeks later), who arrived at the structure of collagen by way of polyproline.

In fact Ramachandran sent his paper to Professor Bernal on *22 April 1955*, six weeks before the editors of *Nature* officially received it, with the following letter:

> Dear Professor Bernal: *22nd April 1955*
>
> I am sending herewith a short article on the "Structure of Collagen", embodying the results of our recent studies, some of which we had the opportunity of discussing with you, when you were here a few months ago.
>
> I would very much appreciate your going through the manuscript, and, if you approve of it, communicating it to *Nature* for publication. We have left out the details, although the structure itself is described at some length, because it is rather complicated. You may amend the article, or cut out some por-

tions, if you consider it necessary, before forwarding it for publication. There are, of course, a number of points still to be worked out, but I hope you would agree that the structure is able to explain some of the principal properties of collagen.

I am particularly grateful to you for the very encouraging interest you showed in our work. In fact, it was your remark regarding the essentially chemical origin of the 640Å spacing that helped us in working out this feature on the basis of our structure.

I shall be grateful for a line in reply when you have had the time to go through the article.

With best regards,

Yours sincerely,
GNR

Bernal, who was not actually working on the structure of collagen, sent the paper to Pauline Cowan of King's College for her comments. She was an investigator working on the structure of collagen, and she wrote the following letter to *Professor Bernal on 1 June 1955*, five weeks after Ramachandran had sent his paper to Professor Bernal.

University of London, King's College
Department of Physics

Strand WC2
1st June, 1955

Dear Professor Bernal:

Thank you for sending the typescript of Ramachandran and Kartha's paper, which I was most interested to read. I am sorry I have taken so long to return it, Whitsun intervening.

Unlike their earlier model, this seems to us a fairly reasonable structure, and should give at least a qualitative fit with the observed diffraction pattern. As a matter of fact, we have ourselves tried to build models along closely similar lines, but they seem to have beaten us to it. Our structure of poly-L-proline (now in press) has a configuration similar to their single chain, although it has a three-fold axis (it resembles their earlier chain). The chief points we have against such models are (1) that as R. & K. themselves point out, there is considerable distortion of the "hydrogen bond angle", (the high value of the NH stretching frequency may support this); (2) that they are complicated—but the formation of this complex system seems to be necessary if the maximum number of hydrogen bonds are to be made.

Whether or not the proposed structure is correct (and I think it is the best one to date), it certainly should be published. There are, however, one or two points that might be made to the authors. They say on page 2 that if the minor helix is composed of L-residues it is right-handed, and the major helix left-handed. It seems to me that they have got their absolute configuration wrong; with L-residues their minor helix should be left-handed. This of course doesn't really matter, but I think the text should be altered. Reference 4 is incorrect. They have produced a hybrid of two papers. The actual reference should be Crick, F.H.C., *Acta Cryst,* 6, 689 (1953)—the paper on coiled coils—which they have muddled with Cochran, Crick, and Vand, 5 (1952).

On page 5 I should substitute "the R side chain of the third residue", or "the side chain of the R-type residue" or "third residue R-group" for "third residue R" to avoid confusion ("R" is usually used to denote side chain, but is sometimes used to refer to the whole residue).

With reference to page 5 last sentence of last para. the 640Å period is by no means always divided into exactly six sub-divisions, although it may be.

The projection of the structure down the fiber axis is rather difficult to sort out. I think it would have been helpful to give a general description of the configuration of the single chain, together with its projection at right angles to the fiber axis, or to give co-ordinates or both.

The model will, of course, have to be tested in detail (it is comparatively easy to get agreement for a single layer line), but it may as well go to press as it stands.

Yours sincerely,
Pauline Cowan

On *6 June 1955*, Professor Bernal replied to Ramachandran as follows:

> Dear Dr. Ramachandran,
>
> I have sent your paper on to *Nature* having made some alterations in it suggested by Dr. Pauline Cowan of King's College to whom I showed it.
>
> If you disagree with the alterations which are outlined in her letter, or wish to make others, this would be possible in the proof stage, assuming *Nature* will agree to publish the paper.
>
> *Yours Sincerely,*
> J. D. Bernal

Ramachandran replied to Professor Bernal on *30 June 1955*.

> Dear Professor Bernal:
>
> Thank you for your letter of June 6th. I could not write to you earlier as I was away from Madras on vacation.
>
> I was very interested to go through the report of Dr. Cowan. We agree with her that the absolute configuration of the helix has been wrongly put and that the minor helix would be right-handed only if the amino acid residues are in the D -configuration. The mistake in the reference was noted by us also after the manuscript was sent to you and I had thought of informing you of it after I received your comments on the paper. The other comments on the report are non-controversial, and I do not think there will be any need to make alterations in the text at the proof stage.
>
> I am highly obliged to you for the trouble you have taken in critically examining the paper.
>
> *Yours sincerely,*
> GNR

It is interesting to note that Professor Bernal chose to give the paper to Pauline Cowan, a competitor of Ramachandran. It is also noteworthy that neither Professor Bernal nor Pauline Cowan raised any objection to the stereochemistry or the amino acid sequence, two major criticisms in the Rich and Crick paper.

A comparison of the three structures, all of which had the common feature of the triple-chain coiled coil first proposed by Ramachandran and Kartha, and some of the ensuing controversy are best described in a review article written by Richard Dickerson.

To paraphrase Ramachandran's thoughts on the discovery of the structure of collagen by the Madras group:

> We studied the chemistry of collagen, its strange amino acid sequence, namely every third residue was glycine. In our case ignorance was bliss, at that time no one had given any importance to the presence of hydroxyproline in the sequence of collagen. Alexander Rich and Francis Crick were also working on the structure of collagen in England, but they did not use any of our experimental data to produce their structure. They used R. S. Bear's data on collagen and built their model with a 3.5Å meridional reflection. One of the greatest advantages we had in Madras was a very clear diffraction pattern of collagen taken by Ambady with a tilted fiber of collagen. That clearly showed that the 2.86Å reflection was indeed meridional and not off meridian as our first structure would have wanted. Astbury reviewed our first paper, apparently he commented that "this young man from India has obtained basically a correct structure for collagen except for some minor details".
>
> Our 1955 paper was sent by the editors of *Nature* to Francis Crick for peer review. Kartha was in Cambridge at the time and apparently found out that either Crick or the editors of *Nature* had sent our manuscript back for revision by sea mail causing a delay in its publication so that Crick's paper on the structure of collagen could be published at about the same time as ours. In any event Rich and Crick's paper was published later than ours.

Ramachandran's statement about the delaying strategy was based on a letter he received from Kartha who left India in October 1955 and gone to the Medical Research Council Laboratory in Cambridge for postdoctoral work. Kartha apparently walked straight into the lion's den, because this was exactly the place where Rich and Crick were working on the structure of collagen. Following is a selection from a letter written by Kartha to Ramachandran on 4 December1955.

> *4-12-55*
> *Cambridge*
>
> My dear Dr. Ramachandran:
> . . . In yesterday's issue of *Nature* there was a paper on collagen by the King's group. They have given neither detailed coordinates nor models. There seems some rivalry between the Kings group and here. Dr. FHC was telling me that their paper has been very unfair to us in their claim of having discovered the structure before us and having had discussed it at the Bristol conference. I do not know what he meant, but the general idea seems to be that the publication of our paper was purposely delayed by months for them to work up our idea after seeing our manuscript! I remember the paper was ready before I left for Bombay, i.e. in April, but it came out only in September. The papers from here came in less than a month. I have not yet gone to King's College but hope to go there very soon. Dr. Randall has asked me to go there whenever I could.
>
> Dr. FHC seems rather unhappy about your note to *Nature* coming at the heels of their paper and suggested that I write to you to postpone it and give them time to modify it!! Probably he may even like to have the final ideas from here and Madras to be put in a combined form . . .
>
> With best regards,
>
> *Yours sincerely,*
> Gopinath Kartha

Readers have to make their own judgment about priorities in the discovery of the collagen structure. It is quite possible that the British scientists did not consider a coiled-coil structure for collagen until they saw Ramachandran and Kartha's manuscript. Neither the Cambridge group nor the King's College group have acknowledged this fact in anything they have written. Yet it is interesting to follow the chronology of the three papers, all appearing within six months in 1955. As Kartha points out in his letter to Ramachandran, it took nearly four months for the editors of *Nature* to accept and publish Ramachandran and Kartha's paper, but less than a month to publish the other two papers by Rich and Crick, and Cowan, McGavin, and North.

In a letter written to Ramachandran on 29 November 1955, Pauline Cowan writes: "When we heard that Rich and Crick had submitted a paper on Collagen I and II, we thought we had better send a note too, since much of our work was parallel and a good deal of it prior to Rich and Crick's. I am afraid our note was sent off in rather a hurry and is not clear. It should be appearing soon in *Nature*."

It is an amazing coincidence that all three groups independently got the idea for a coiled-coil structure at about the same time within a period of six months. The British scientists were working for a much longer period on collagen than Ramachandran and Kartha. Ramachandran has justifiably felt that the British scientists did not give him the proper credit or recognition that he deserved for his fundamental and original contribution of a coiled-coil structure for collagen. He believes they may have used his idea and, on top of that unjustifiably criticized his collagen structure. It is perhaps too cynical to conclude that some of those working on collagen in England at the time simply could not accept the fact that two scientists from one of their former colonies could make such an outstanding contribution in such a short time.

Sir Isaac Newton may have been one of the greatest scientists of all time, but he was also the scientist who began the tradition of priority in published results, a sentiment that has been perpetuated ever since. The intent of doing research primarily for discovering nature's hidden truths to be applied for the good of humanity may have taken a back seat after Newton.

Undoubtedly Crick is one of the most brilliant molecular biologists of this century, and he certainly deserves credit for his pioneering work on the structure of DNA. His work on the theory of diffraction by non-integral helices was of immense help for Ramachandran and Kartha in comparing the observed and calculated diffraction patterns for collagen, and was another classic paper in biophysics.

In their attempts to be the first to discover the structures of important biological macromolecules, one sees an interesting chain of triumphs and tribulations. Sir Lawrence Bragg, who had already made a name for himself by discovering the basic principle of X-ray diffraction and was immortalized by a law that carries his name, was disappointed because he was not the first to discover the structure of the alpha helix; Linus Pauling got that honor. Pauling was disappointed that he did not discover the double-helical structure of DNA; James Watson and Francis Crick shared that honor. Crick was perhaps disappointed that he was not again the first to discover the triple-helical coiled-coil structure of collagen; Ramachandran and Kartha certainly deserve the credit for that discovery.

8. Stereochemistry of Polypeptide Structures

The rejection of their collagen structure by Rich and Crick had a profound effect on Ramachandran and his coworkers in Madras especially on Kartha. In one way it was a blessing in disguise because it paved the way for Ramachandran's next major contribution when he attempted to answer criticisms aimed at his collagen structure. Recall that the most severe comments by Rich and Crick were targeted toward the short, non-bonded distances in Ramachandran's model. Computers had not arrived in Indian science and they even lacked sophisticated model- building facilities in Madras. In fact, Kartha measured the bond distances in their crude models using pieces of string or the ribs of coconut leaves!

A very smart young graduate student by the name of Sasisekharan joined Ramachandran's department in Madras about that time. Sasisekharan obtained a B.Sc.(Honors) degree in physics, exactly as Ramachandran himself had done earlier. In order to do research for a Ph.D degree in Madras University, students first had to obtain a master's degree in either X-ray crystallography or in theoretical physics. Sasisekharan first completed his master's degree in X-ray crystallography, then began working for his doctorate degree under the supervision of Ramachandran. He undertook the investigation of the structures of poly-L-proline and poly-L-hydroxyproline, which are two collagen-like polypeptides. Sasisekharan prepared fibers, took their X-ray diffraction patterns, and started model building. The final model is best described as a polyproline helix, in which the three separate polyproline chains are related by a three-fold screw axis.

Completing a degree in those days required the approval of the Ph.D. dissertation by three external examiners, chosen from outside India. A copy of the dissertation was sent to each examiner, who had three months to read and send the evaluations to the University. Sasisekharan's thesis was highly commended by all the three examiners, one of whom was Max Perutz, the well-known molecular biologist in Cambridge, England, who won the Nobel Prize for discovering the structure and function of hemoglobin.

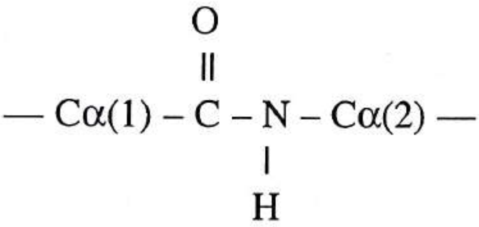
Sasisekharan obtained his doctorate in 1960 working under the guidance of Ramachandran. He then joined Ramachandran's department as a lecturer (equivalent to an assistant professor in an American university) to continue his research on fibrous proteins. This is a common practice among Indian students who, after obtaining their doctorates apply to universities in England or United States for postdoctoral fellowships. While waiting for responses, they often continue their research either on the same or on a new project in the same department where they obtained their Ph.Ds. Often this is not desirable because the research supervisor is likely to continue treating them as his students. Similarly the former students would continue to treat the supervisor as a professor rather than as a colleague. This was especially true in Ramachandran's department because of his reputation as an established scientist.

However, collaborative research with Sasisekharan was very productive and resulted in another innovative breakthrough by Ramachandran in the field of molecular biophysics. Stung by the criticism of short interatomic contacts in his collagen structure, Ramachandran and Sasisekharan decided to conduct a systematic survey of the literature for data on non-bonded contact distances between atoms within and between molecules in all known organic crystal structures. They hoped to answer the following questions: How closely do non-bonded atoms approach one another in organic and biological structures? Is there a range in the observed distances? Is it possible to systematically generate all possible structures of polypeptides based on the limits of the non-bonded interactions alone? Can this information be used to systematically delineate and predict the most probable structures for biological macromolecules?

Together they designed a general method for describing the stereochemical criteria for polypeptide structures and proteins. They presented what has come to be known in biochemical literature as the "Ramachandran phi-psi diagram" or simply "Ramachandran plot." It provides a rational basis for describing all stereochemically possible structures of polypeptides. Even though the significance of this work was not realized or appreciated at the time, the study of stereochemical criteria has since become one of the most important areas in the investigation of protein structures.

Another young man by the name of Ramakrishnan also had joined Ramachandran's group in Madras as a graduate student. Ramakrishnan was an indefatigable worker and was primarily responsible for doing all the calculations that went into the drawing of the Ramachandran phi-psi diagram. These calculations were done on an electric desk calculator, work that Ramachandran describes as a "Himalayan task." In fact, Ramakrishnan has continued this work on stereochemical criteria of polypeptide chains for over three decades. All the three scientists must share the credit for the phi-psi diagram.

Proteins, like collagen, are linear polymers of twenty different kinds of amino acids. The basic structure of amino acids found in naturally occurring proteins has already been described. Two amino acids are joined together by what is known as a "peptide bond"—the chemical bond formed between a carbon atom of the carboxyl group (COOH) of one amino acid and a nitrogen atom of the amino group (NH_2) of the next amino acid. In this process a water molecule is eliminated. The NH and the CO groups interact with each other so as to produce a partial double-bond character to the C— N bond. Consequently, the following six atoms in two consecutive amino acids form a rigid planar group called a "peptide unit."



$$-\,C\alpha(1)-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle H}{|}}{N}-C\alpha(2)\,-$$

The group of atoms —Cα(1)— C — N — Cα (2)—repeats many times in a polypeptide structure. They form the backbone of a polypeptide chain, usually referred to as the "main chain." Atoms of the side chain branch off from the alpha carbon atom of each amino acid in the main chain. In 1953, Pauling and Corey used all available data from known crystal structures of simple amino acids and other peptides to define the bond distances and bond angles in the planar peptide group. These dimensions have become the standard for building models of protein structures.

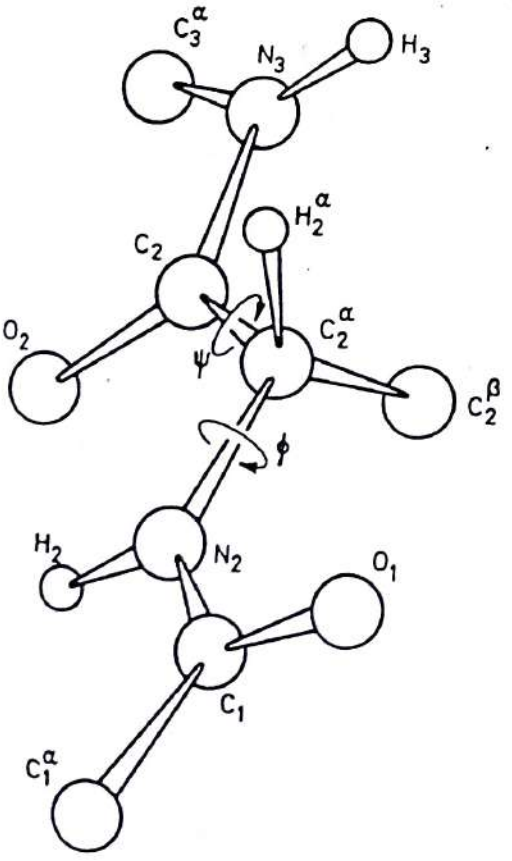


Figure 10: Diagram showing the dihedral angles ϕ and ψ (see later for the nature of ω).

Three covalent bonds are present between two alpha carbon atoms in the planar group described above. Two of these, Cα(1) — C and N — Cα(2), are single bonds while the third, C — N, has some partial double-bond characteristics as indicated by its length, which is shorter than a normal single-bond distance and longer than a true double-bond distance. A single bond is flexible and allows for free rotation about that bond. However, double and triple bonds are more rigid and do not allow such free rotations.

The angles of rotation about each single bond can vary between 0 and 360 degrees. Each set of rotations will generate new positions for all atoms in the polypeptide structure on either side of the bond. Not all such structures are physically possible or chemically meaningful, because they may result in unacceptable stereochemical overlaps between two or more atoms. Atoms are not simple points, they have a definite size. They are assumed to be spheres and their radius is called the "van der Waals radius". No two non-bonded atoms can approach one another closer than the sum of their van der Waals radii.

Ramachandran, Sasisekharan, and Ramakrishnan set out to identify those rotation angles that would generate acceptable structures for polypeptides. Scientists working in this field knew about the geometry of a planar peptide bond and the constraints imposed by partial double bonds. The concept of using these ideas to generate all the possible structures was quite innovative and very original.

Ramachandran used the notations *phi* and *phi′* to describe the two rotation angles; phi specified the angle of rotation about the Cα — N bond and phi′ specified the angle of rotation about the Cα — C bond. They also described a standard reference point to define the zero degree angles for phi and phi′. The notation they used actually conformed with the accepted notation in the literature of the organic chemistry of biopolymers. Subsequently, the designations for the angles were changed to phi and psi, respectively, by an international commission described later in this chapter.

Dihedral angles are angles that describe the relative orientation between any two planes. If the dihedral angles of rotation (phi and psi) between the two peptide units are known, it is possible to calculate the positional coordinates of all atoms in the main chain of a dipeptide. This is because the peptide units have a planar structure and the relative positions of all atoms in the peptide planes that undergo rotation are already established. In other words, the three-dimensional structure

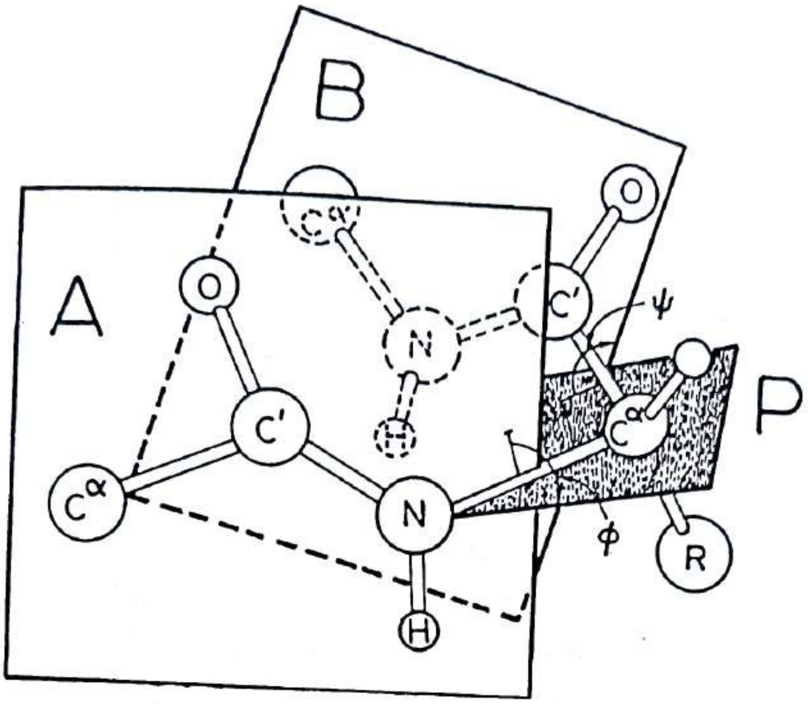


Figure 11: Diagram showing a general conformation (ϕ, ψ) about an α-carbon atom Cα. The shaded plane (P) contains the atoms N, Cα, C′ and the bonds N–Cα and Cα–C′ about which the rotations ϕ and ψ are made. The other two planes A and B represent the planes of the two linked peptide units. A clockwise rotation ϕ about N– Cα brings the plane A to the plane P and a clockwise rotation ψ about Cα–C′ brings the plane P to the plane.

of the main chain atoms of a dipeptide may be completely described if two dihedral angles between the two peptide planes are known. By extension, it is possible to describe the complete structure of all main chain atoms in a large polypeptide chain containing N amino acids using 2 (N - 1) sets of (phi, psi) angles.

Ramachandran asked the following question: Would all possible values of phi and psi produce chemically acceptable and stereochemically meaningful structures? A cursory examination of models of structures generated after various rotations of a dipeptide reveals that not all combinations of phi and psi generate physically meaningful structures.

In 1957, Ramachandran and Sasisekharan analyzed all published reports of amino acids, peptides, and other relevant organic compounds and cataloged the observed non-bonded contact distances between atoms in their structures. Sasisekharan used stereographic projections to display the different observed dihedral angles. Preliminary findings were included in Sasisekharan's doctoral thesis submitted in 1959.

They defined two possible limits for the non-bonded distances that they called (1) "normally allowed limits" and (2) "extreme limits." The former is such that if all interatomic distances are longer than the nor-

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mal limit, there are no restrictions on that structure and it is very likely to occur. They called it a "fully allowed" or "normally allowed" conformation. However, they found that if there are compensating features in a crystal structure such as hydrogen bonds or other favorable effects in the vicinity of some atoms, then any contact distance as low as the shorter extreme limit may be observed. Therefore, if some contact distances lie between the normal and extreme limits, such a structure is still possible, but would be less stable than a fully allowed conformation. On the other hand, a structure with one or more non-bonded distance less than the extreme limits is very unlikely to occur and hence would be disallowed.

They followed a very simple procedure. They generated structures of dipeptides for all combinations of the two dihedral angles phi and psi. For each such structure they calculated all bonded and non-bonded contact distances between different atom pairs. If any two atoms approach one another closer than the sum of their van der Waals radii, then the two atoms will overlap and will cause steric hindrance. Such a structure is stereochemically impossible.

Ramachandran and Sasisekharan set out to identify these structures for proteins and polypeptides. They immediately realized that a systematic survey of all possible structures would involve a tremendous amount of calculations. Ramakrishnan used a desktop electric calculator to calculate the interatomic distances for dihedral angles varying in intervals of 10 degrees from 0 to 360 degrees. They displayed their results in the form of a conformational map in which they outlined regions of phi and psi angles for which structures occurred without any two non-bonded atoms overlapping on one another. These were the fully allowed conformations. Structures in such regions did not have any non-bonded contacts below the "extreme limits." Then there were partially allowed conformations in which the non-bonded distances were between normal and extreme limits. The allowed regions became more restrictive when amino acid residues other than glycine were involved. Recall that glycine is the smallest amino acid present in proteins and has only a hydrogen atom for its side chain. The presence of larger groups of atoms in the side chain forbids some allowed conformations as they would make non-bonded contacts below the extreme limits.

The first paper announcing these results was published in the proceedings of a symposium organized by Ramachandran at the Central Leather Research Institute in Madras in 1962. Sasisekharan was the

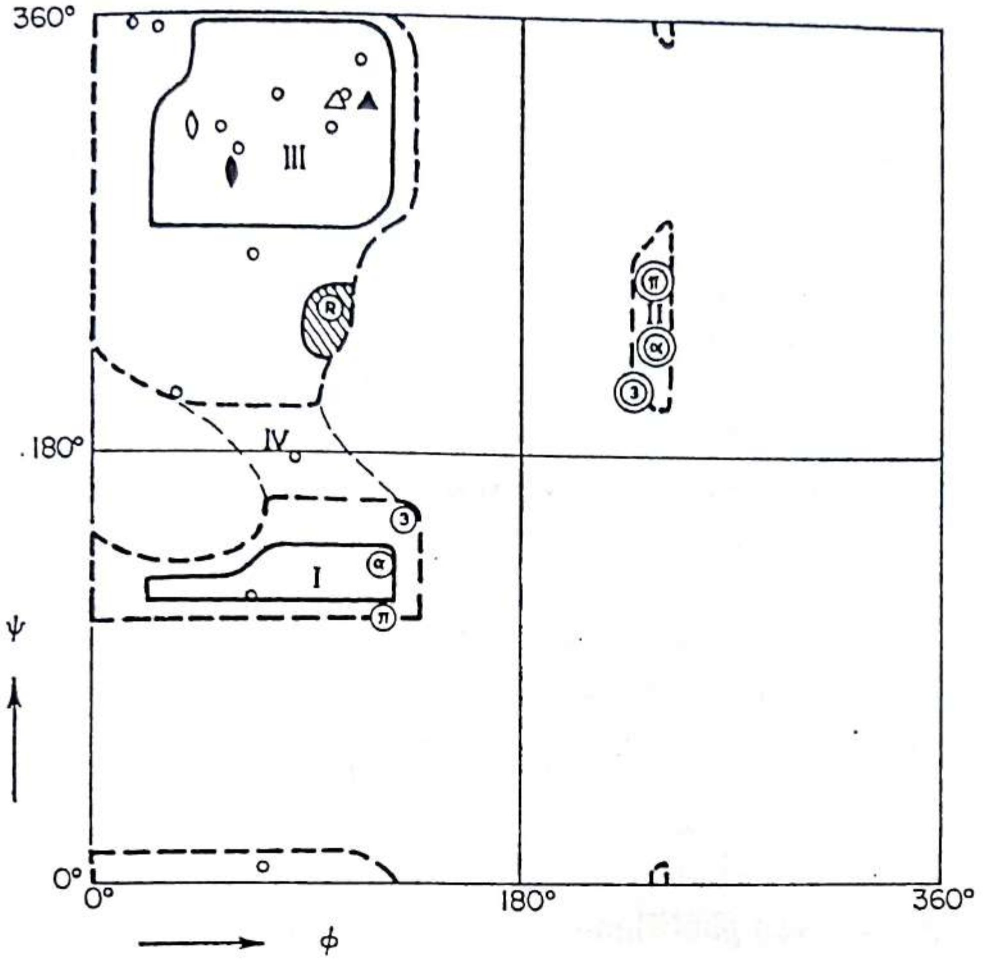


Figure 12: Ramachandran-Sasisekharan-Ramakrishnan phi-psi plot showing fully allowed conformations for polypeptides. Dihedral angles resulting in standard secondary structures such as the alpha helix are indicated in the plot.

single author of the paper, even though the work was done jointly with Ramachandran and Ramakrishnan. The delay in publication combined with the criticism of his paper on collagen must have made Ramachandran somewhat skeptical about sending this paper to a journal in England. Nevertheless, a second "paper" was indeed published in the *Journal of Molecular Biology* in 1963 by all the three authors—Ramachandran, Ramakrishnan, and Sasisekharan, in that order. Not a full article, it was published instead in the "Letters to the Editor" section of the journal. Some skeptics in the Madras group believed that Kendrew, who was the editor of the *Journal of Molecular Biology* may not have fully recognized the significance of what must have appeared to him as a simple and an inconsequential article. But that article contained some very interesting and fundamental results, perhaps arriving on the scene well before its time.

Protein structures were just being determined at the time and the significance of Ramachandran's analysis probably did not draw too much attention. But the ideas and results presented in these two papers were simple and elegant. Ramachandran predicted the allowed combinations of rotation angles phi and psi for the structure of a polypeptide chain. Naturally Ramachandran wanted to verify the results of his prediction when the structure of the first protein, myoglobin, was published and spatial coordinates of all atoms became known. Proof that the experimentally determined values of phi and psi in a globular protein lie within the predicted regions of the Ramakrishnan-Sasisekharan conformational map would have been most gratifying. However, in those early days of protein crystallography, scientists were reluctant to share the coordinates of protein structures with other investigators in the field. They were apprehensive that others might use their coordinates, do calculations, and publish results. They believed that having solved the structures, only they were entitled to do such calculations and reap the benefits themselves. In any event, Ramachandran's attempts to obtain a copy of the myoglobin coordinates from John Kendrew were not successful at least in the beginning. Nowadays, investigators have to deposit coordinates of all atoms in a new structure in a Protein Data Bank before even publishing their structures in journals.

Those who had access to coordinates of protein structures used them to calculate the phi and psi angles and compared them with predictions of the Ramachandran-Ramakrishnan-Sasisekharan conformational map. Almost all the calculated angles between consecutive peptide planes were found to be within the allowed regions of the map. Whenever a dihedral angle was outside the predicted range, it invariably belonged to a glycine residue which, as mentioned above, has more conformational freedom. Protein crystallographers were pleased with this result, as it was considered excellent proof that their structure was stereochemically acceptable. Ramachandran and his coworkers were happy with the same result because their assumptions and rationale for the prediction of polypeptide conformations were indeed justified.

This triumph was appropriately recognized when the leading Harvard protein chemist, John Edsall, invited Ramachandran to contribute a detailed review article for publication in the *Advances in Protein Chemistry* in 1968. Ramachandran invited Sasisekharan to coauthor the review, he would have gladly included Ramakrishnan, as he was also part of the group, but the latter was busy writing his doctoral thesis. The review gave well-deserved exposure to this original

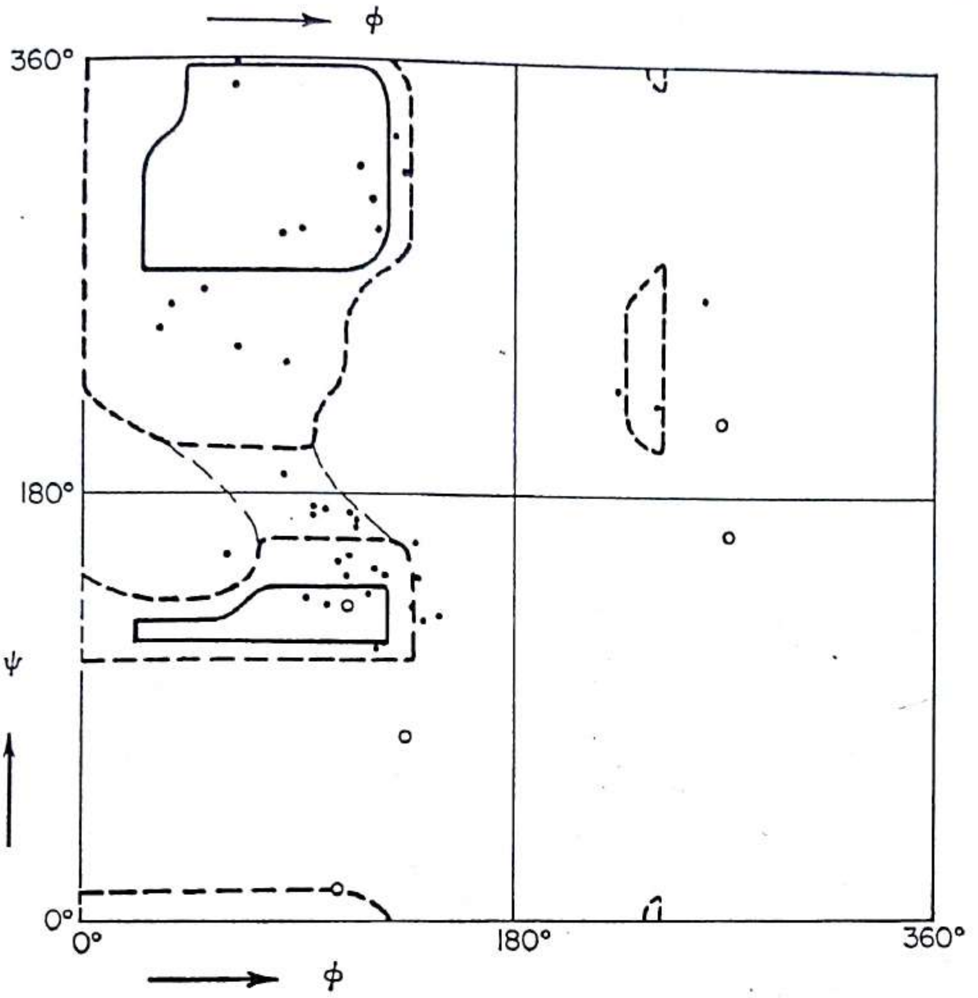


Figure 13: Phi and Psi angles calculated using the experimentally determined coordinates of the myoglobin structure. Only the angles for residues not on the alpha helix are shown. Points outside the allowed region predicted by Ramachandran and coworkers are for glycine residues for which hydrogen is the side chain atom.

piece of work from India to the rest of the scientific world. In 1969, Richard Dickerson and Irving Geis described the results of the conformational map in their classic book on the *Structure and Action of Proteins* published by Harper and Row. Dickerson was the first to use the name the "Ramachandran (phi, psi) diagram." None of the three original discoverer's referred to their map by that name. Perhaps the proper name should have been "Ramachandran-Ramakrishnan-Sasisekharan (phi, psi) diagram." Sasisekharan had just obtained his doctorate degree, Ramakrishnan was still working toward his doctorate, and both were working in Ramachandran's laboratory. Yet all of them were part of a single team, and the research was truly a joint effort. It was a collaborative project in which ideas, data, and calculations could not be attributed to any single person. Though the diagram now is most commonly associated with Ramachandran, what's in a name? (as the saying goes).

One of the most important related discoveries published by Ramachandran and his coworkers at the time was what is currently well known as the β turns or β bends in polypeptide structures. A young graduate student named Venkatachalam first made the discovery of these types of structures in Ramachandran's laboratory in 1967. He was interested in systematically investigating all possible structures of tri- and tetrapeptide units and discovered that at least three favored conformations of tripeptides were possible and all were stabilized by hydrogen bonds. These structures represented regions where a peptide chain would make a U-turn, forming the beginning of a pair of anti-parallel beta-pleated sheets. They neither called them beta turns at the time nor did they have any means of proving the validity of their predictions in structures of proteins. They were, of course, delighted to see such turns when the tertiary structure of the first protein, myoglobin, was published. The results were published in Venkatachalam's Ph.D. thesis. Professor Harold Scheraga of Cornell University, one of the pioneers in the field of polypeptide conformations was one of the external examiners of the thesis. Professor Scheraga did not hide his delight after reading Venkatachalam's thesis; he declared it came up to his highest standards and easily comparable to the best thesis from his own country.

During the 1964 Biochemical Congress in New York, a meeting was arranged to discuss the general question of accepting or revising the standard notation and nomenclature for dihedral angles in polypeptide chains. Ramachandran was one of the leading participants in that discussion. The congress recommended two changes: (1) change of nomenclature of phi and phi′ as adopted by Ramachandran's group to phi and psi, and (2) a change of origin of the phi-psi plot from the bottom left-hand corner to the center of the diagram. The angles along the x and y axes ranged from -180 to +180 degrees instead of from 0 to 360 degrees as in the original paper. There was a very dynamic discussion and Professor Flory, who later won the Nobel Prize in 1982, stood firmly by the IUPAC-IUB notation (International Union of Pure and Applied Chemistry-International Union of Biochemistry) which was the same as the convention used in the original phi-psi map. On the other hand, all persons working in the field of biopolymer research, including Professor Scheraga, wanted the revised convention for polypeptides. Ramachandran's group had considerable experience in this field and he was for the development of a convenient nomenclature for biopolymers that would be acceptable for all workers in the field. Professor Edsall, who chaired the meeting, felt that both suggestions were acceptable and asked Professors Kendrew and Ramachandran to prepare suitable rules for all polypeptides. Kendrew chaired the commission and the rules—known as Edsall-Kendrew rules—were published simultaneously in four journals, *Biopolymers*, *Journal of Molecular Biology*, *Biochemical Journal* and *Biochemicà Biopysica Acta*. Within one year every laboratory in biopolymer research, molecular biophysics, conformational theory, and bioorganic chemistry had adopted the new rules set forth by the commission, which were of great utility especially to newcomers in the field.

Ramachandran had taken such great interest in this work on nomenclatures that several years later when a similar need arose for a committee on nomenclature of nucleic acids and nucleotides, he was asked to chair that committee. He consulted his friends and colleagues working in the field and realized that the problem was much more complex than polypeptides, so he declined the request to chair the committee. In 1979, Professor Oster of Vienna, Austria, suggested that Ramachandran should consider chairing a much wider committee on nomenclature of proteins, nucleotides, and polysaccharides. Since Ramachandran had stopped working on this aspect of molecular biophysics altogether, he declined this request too. It is of interest to note that while it took only two years to write the rules and conventions for proteins and polypeptides, it took over five years to do the same for nucleotides and another three years for polysaccharides.

9. Calcification of Collagen

Studies on collagen and stereochemical conformations were not the only projects going on in Ramachandran's department. Ramachandran was a crystallographer and there was some first-rate crystallography going on in Madras. K. S. Chandrasekharan and M. A. Lonappan joined Ramachandran's lab in Madras during the very early stages; the former continued his work on dynamic X-ray reflections from potassium chlorate crystals and the latter began working on the thermal expansion of sodium chlorate crystals.

One important project in Ramachandran's laboratory that apparently was too far ahead of its time started with his ideas on the structural relationship between collagen and bone. Gopalakrishna Ambady was a graduate student in the lab who excelled in laboratory work and experimental techniques. It was his X-ray diffraction photograph of tilted collagen fibers which swiftly suggested to Ramachandran and Kartha that collagen had to be a triple coiled-coil structure. Ambady performed an elegant experiment by immersing fibers of collagen in an emulsified salt solution. The salt would spontaneously crystallize on the fibers. Several insoluble compounds like silver oxide, white lead, calcium fluoride, and calcium carbonate could also be crystallized inside collagen fibers by keeping them in solutions containing suitable concentrations of the required ions. When hydroxy apatite, a complex salt of calcium phosphate, was used as the salt, it also crystallized on the fibers. The diffraction pattern from such a fiber was compared with that from bone specimen. The resemblance between the two was striking, but for the greater sharpness of the pattern observed from the synthetic specimen, showing that the particle size of the hydroxyl apatite crystals is much larger. The emerging hypothesis was that bone was analogous to a calcified form of collagen.

Ramachandran wanted to further study this phenomenon and assigned this problem to M. S. Santhanam, another Ph.D. student. Unfortunately, Santhanam was only a part-time student in the department. Because he was teaching in a local college, he could not spend sufficient time on the project, nor did Ramachandran have enough time to supervise the project. When he finally finished the work on the calcification of collagen as well as the structure of elastin, another important connective tissue protein, Santhanam thought that he had collected ample evidence to prove this hypothesis. However, his Ph.D. thesis was submitted twice and was rejected on both occasions by the external examiners—Professor Bernal of Birkbeck College and Sir John Randall of King's College, both in London. Even though Bernal was in favor of approving and recommending a doctorate for Santhanam, apparently Randall completely disagreed with the conclusions presented in the thesis.

This was a devastating blow to the morale of every one in the department and the atmosphere was tense. A sense of total despair and helplessness prevailed, as the examiners of the thesis were 6,000 miles away and there was no discussion, defense, or rebuttal once their decision was communicated to the vice chancellor of the university. To quote Ramachandran: "You may be surprised by the fact that the universities in India never allow a professor to see the reports written by the so-called outside examiners on the theses of their students." Ramachandran felt that Santhanam was more of a chemist than a crystallographer and perhaps did not properly understand the physics of diffraction or Fourier transforms. Little did he realize that his own ideas on calcification of collagen might have been too far advanced for its time. Again to quote Ramachandran: "Many years later, when I was in the United States, scientists were trying to do exactly similar work in the Massachusetts Institute of Technology!"

The question of whether bone formation is a process of calcification of collagen is still under active scrutiny.

10. Anomalous Dispersion

Anomalous dispersion is a phenomenon in X-ray diffraction that occurs when X-rays are scattered from the crystal of a molecule in which one or more atoms have an absorption frequency close to that of the incident radiation. When this happens, the anomalously scattering atom in question will selectively absorb the incident X-rays and will scatter in a characteristic way, resulting in a phenomenon called "anomalous dispersion." Reflections with Miller Indices of the type h,k,l and -h,-k,-l, called Friedel pairs, which normally have identical intensities, will no longer be the same. The difference in intensities between each Friedel pair is called the "anomalous difference," or the "Bijvoet difference," named after the pioneering work of the Danish scientist Bijvoet and his collaborators.

Normally results of X-ray analysis cannot distinguish between a structure and its mirror image, because both give identical diffraction patterns. Bijvoet and his collaborators showed that it is possible to use anomalous dispersion to distinguish between the two configurations, or to determine the so-called absolute configuration of a molecule. (Bijvoet, J. M.(1949) *Proc. Acad. Sci.*, Amst. 52, 313, Bijvoet(1954), *Nature*, 173, 888).

Ramachandran saw the original paper by Bijvoet during one of his weekly visits to the university library and suggested it to his student K. S. Chandrasekharan, who had joined him as a graduate student under a leave of absence from the Atomic Energy Commission (now Bhabha Atomic Research Center). Together they began to study sodium chlorate and established its absolute configuration using anomalous dispersion. In Chandrasekharan's words, sodium chlorate became "the Indian crystal that laid golden eggs."

Chandrasekharan recounts a story of how during one of his experiments a small fly sat on the crystal of sodium chlorate that he was using to obtain the X-ray diffraction data. He had to mount a completely new crystal and repeat all the measurements. Both Ramachandran and Chandrasekharan were happy that at least they had two sets of measurements of the same diffraction data, which proved statistically more accurate.

Anomalous dispersion measurements have also been used to calculate phase angles for all the reflections in a diffraction pattern. The phase angle of each reflection constitutes the second most important quantity necessary for calculating the electron density map of molecules in crystals, the first being the structure amplitude which is proportional to the square root of the experimentally measured intensity of a reflection. Electron density maps are used to build models of the molecules and to solve the crystal structure.

The anomalous dispersion technique was first applied for the solution of the phase problem in 1956 by Ramachandran and Raman, (Ramachandran, G. N. and Raman, S.* (1956) *Current Science* (India), 25, 348) a graduate student in Ramachandran's laboratory. They applied it to the known structure of ephedrine hydrochloride and showed that the correct choice of phase angle was closer to the phase of the anomalous scatterer. The structure of this molecule had been determined earlier in 1954 by David Phillips using the standard heavy atom method (Phillips, D. C. (1954) *Acta Cryst.* 7, 159). Raman then applied the anomalous dispersion method to obtain phase angles and successfully determine the crystal structure of lysine hydrochloride for which no previous structural data was available. (Raman, S. (1959), *Z. Kristallogr.* 111, 301).

The Madras group used the film technique to record and measure the intensities of all reflections in any diffraction pattern. This technique is still in use in many laboratories; although films are now digitized using automated computer-controlled scanners. Because computers were not available in Madras at the time, the intensities were estimated visually by comparing each reflection on the film with a special strip of film that contained a set of standard spots. The standard spots were recorded by exposing the strip to a preselected reflection from a crystal once, twice, three times, four times, etc. The successive spots would have a relative intensity of 1, 2, 3, 4, etc. The strip with the standard set of spots is placed on top of the diffraction film whose intensities are to be measured. Each reflection is compared with successive standard spots until a match is found between the two. This gives a quantitative, although subjective, measure of the relative intensity of each reflection. In the Madras laboratory, it was a common sight to see students sitting near a window during the day holding films up to the daylight to measure the intensities of reflections on their X-ray diffraction photographs. Luckily, Madras has bright sunny days most of the year!

*No relation to Sir C. V. Raman

An alternative way to collect diffraction data uses ionization detectors, which were sadly not available in Madras laboratory at that time. Measurements of anomalous differences between Friedel pairs of reflections require very accurate experimental methods, since the differences are very small and often fall within the range of experimental errors. In spite of that, Ramachandran's young and determined student Raman measured the intensities of Friedel pairs from crystals of lysine hydrochloride, calculated phase angles for all observed reflections, computed an electron density map, and determined its crystal structure. Lysine is one of the amino acids commonly found in proteins. Since then the anomalous dispersion method has been successfully used in many cases for solving the phase problem in X-ray crystallography around the world.

The research accomplishments on collagen and conformational analysis of polypeptide chains had clearly placed the Madras department on the map of molecular biophysics. Ramachandran had established himself as a pioneer in the field, and he was not yet 40 years old. The progress in science in his laboratory was of world-caliber and easily comparable to that in any other well-known laboratory in England or the United States. There were, however, many frustrations among the Madras scientists. It was hard to do good science in India under the meager economic conditions and inadequate laboratory facilities. It was even harder to get the deserved recognition from peers in the Western Hemisphere, despite producing first-class results. It took an inordinately long time to get their results published in reputable foreign journals. The postal delay in transmitting and receiving manuscripts alone was formidable. There was a general suspicion that referees in England and the United States adopted different standards for manuscripts submitted from India and other developing countries. Publication of the results in Indian journals was quicker, but those journals were not widely read and often unavailable in many laboratories in England and the United States.

11. Fourier Syntheses and Other Projects

In addition to the research already mentioned, Ramachandran and his colleagues in Madras were actively working on a series of problems associated with Fourier analysis. Fourier analysis, or Fourier transforms, is an essential mathematical tool used in the investigation of any periodically varying phenomenon, such as the propagation of waves or the highly ordered distribution of molecules in a crystal. His father had initiated Ramachandran into the theory of Fourier analysis when he was an undergraduate, and later Professor Raman helped him to achieve a more rigorous insight. He was absolutely fascinated by its applications and power to solve all kinds of problems. As a practicing crystallographer, he was familiar with the use of Fourier synthesis in obtaining electron density maps of molecules in crystals.

Ramachandran applied his knowledge of Fourier analysis to the study of a new problem in crystallography, namely determining the complete structure of a molecule when only a part of it is known. The so- called "heavy atom method" is one such method well-known to crystallographers, who frequently use it to determine structures of small molecules containing one or more heavy atoms.

The amplitude of the X-ray waves scattered by atoms in a molecule depends on the number of electrons present in each atom. Most organic molecules are made up of carbon, nitrogen, and oxygen each having 6, 7, and 8 electrons, respectively. Therefore, each atom will scatter by approximately the same amount. If, however, the structure contains a chlorine atom, for example, then it is considered a heavy atom, as it contains seventeen electrons, and will scatter X-rays more strongly than a carbon or nitrogen. Proteins contain thousands of carbon-like atoms. In this case mercury, platinum and uranium are considered heavy atoms.

The heavy atom method makes use of the strong scattering produced by the heavier atoms in the molecule. Once the positions of heavy atoms in the unit cell of the crystal are determined, they are used to calculate the phase angles of all reflections, which in turn are used to compute a preliminary Fourier map. This map is called "a heavy atom phased Fourier" and it gives an approximate distribution of the electron density of the complete molecule in the crystal. The map will usually show peaks of electron density at positions corresponding to where the remaining lighter atoms are present in the structure. This procedure is used iteratively, with new improved phase angles calculated in each cycle using coordinates of the heavy atom and the newly determined light atoms in the structure. After several such iterations the coordinates of all atoms in the molecule or the entire structure would be determined.

Ramachandran asked the question: Can one formulate other forms of Fourier analysis that can be used to unravel the complete structure of a molecule when only a part of it is known? The known part need not be restricted to heavy atoms as in the heavy atom method. Suppose a structure does not contain any heavy atoms, but is made up of only light atoms. If the structure of a part of it is known, how can this information be used to determine the rest of the structure? His investigations led to: (1) a novel way of interpreting results of any Fourier calculation in crystallography (2) the derivation of a number of interesting combinations of coefficients that might be used for calculating new types of Fourier syntheses; and (3) a systematic procedure to predict and analyze the structural features in such maps.

Ramachandran and Srinivasan, who was among the first batch of graduate students in Madras, began to develop new methods and new types of Fourier syntheses. Fourier syntheses in crystallography is a calculation done in three variables x, y, and z or three dimensions. The summation is carried out using all the Miller indices of reflections in the diffraction pattern. Thus, if 10,000 reflection intensities have been measured from a single crystal, then the electron density at any one point in the crystal is obtained by the addition of at least 10,000 and sometimes 20,000 numbers. These numbers are obtained by multiplying two quantities: one is related to the intensity of each reflection; the other is a trigonometric function, such as the sine or cosine of the phase angle for that reflection. The amplitude and the phase angle of a reflection are called the coefficients of the Fourier summation. The significance and the interpretation of the peak positions in such a summation depend on the nature of the coefficients that are used in the calculation of the Fourier map.

If, for example, experimentally measured intensities of all reflections are used as amplitudes and the phase angles for all reflections are set equal to 0 degree, then the resulting Fourier syntheses is called a vector map, or the "Patterson synthesis." The peaks in the Patterson map will occur at positions corresponding to "vectors" between atoms in the structure, taken two at a time. They are different from the actual coordinates of the atoms. When square roots of the experimentally measured intensities are combined with phase angles calculated from known positions of heavy atoms, the resulting Fourier map will correspond to electron density in the crystal, such a map is called the "the heavy atom phased electron density map."

While the heavy atom method was successful in general, no attempt had been made to test whether this was the best way of making use of the known partial structure. Two basic types of Fourier syntheses defined by Ramachandran were the "modulus structure" and the "phase structure." The former uses only the modulus of the structure amplitude as coefficients in a Fourier summation, while the latter uses a combination of structure amplitudes and phase angles as coefficients. This led to the question: Which is more important in calculating a correct electron density distribution in a crystal, amplitudes of reflections or their phase angles? Using various combinations of coefficients, Ramachandran and Srinivasan concluded the overwhelming importance of phase angles in revealing details of a crystal structure.

Ramachandran and Srinivasan systematically analyzed different combinations of experimentally measured and calculated values for coefficients. The latter is computed from knowledge of partial structures, i.e., coordinates of some heavy or light atoms in the structure. They called them α, β, γ and α', β', γ' syntheses and in each case showed how one could derive the positions and strengths of peaks in the resulting Fourier map. They performed various tests to see which Fourier analysis was superior in revealing the unknown atoms in the structure. Some of these analyses were being routinely used in Ramachandran's laboratory to determine unknown structures.

Ramachandran extended the Fourier analyses to include isomorphous and anomalous differences when appropriate and defined two new types of syntheses, β_{iso} and β_{ano}. Anomalous differences occur between Friedel pairs of reflections (h,k,l) and (-h,-k,-l). Isomorphous differences occur between intensities of same reflection (h,k,l) from two isomorphous crystals that differ by having some atoms replaced by other atoms in the same location in the two molecules. Isomorphous crystals often have same unit cell size and symmetry, but different intensity distributions in their diffraction patterns. The isomorphous and the anomalous differences used in combination were found to be superior to their use in isolation.

The analysis reported by Ramachandran and Srinivasan was not limited to the new types of syntheses described by them, but could also be used to understand and interpret any general type of Fourier analysis. The results of this research were reported in a number of timely papers, and they finally culminated in the publication of a detailed book by Ramachandran and Srinivasan called *Fourier Methods in Crystallography* published by Wiley Interscience in 1970.

Ramachandran's department had grown in size during the 1960s. Every year three or four students were recruited for the Ph.D. program from among those who completed the master's degree in X-ray crystallography or theoretical physics. Ramachandran had an interesting philosophy for running his department. To quote him: "I was following my teacher's philosophy in that each student must be given a different problem. S. Raman was developing anomalous dispersion to solve the phase problem; V. Sasisekharan was solving the structure of polyproline; R. Srinivasan was to determine the structure of tyrosine hydrochloride and investigate a number of theoretical problems related to Fourier syntheses; and E. V. Krishnamurthy was designing analog computers."

This work on analog computers was completely different from everything else that was going on in Ramachandran's laboratory. E. V. Krishnamurthy was another one of the first group to join Ramachandran as graduate students with a stipend of 56 rupees a month. This was a ludicrously small amount and he complained to Ramachandran of his inability to survive in Madras on that kind of money. Vice Chancellor A. L. Mudaliar, fully aware of Ramachandran's reputation as a respected scientist, readily agreed to his request to create a new position of instrument technologist to service and maintain instruments in different science departments of the university. The salary was set at 150 rupees a month and Krishnamurthy was hired to fill this position. Again on Ramachandran's recommendations, he was also allowed to do research in addition to working as an instrument technologist.

Krishnamurthy had an interest in numerical analysis and instrumentation development. He undertook the design and construction of what Ramachandran called a "digito-analog computer" for solving linear simultaneous equations by an iterative procedure. In this procedure, you start with approximate solutions for the variables in the equation and refine the solutions in each cycle until there is convergence to the true solutions for the simultaneous equation. It operated on analog storage but then used digital methods. Together Krishnamurthy and Ramachandran worked out the logical and electrical circuits of various computer components and Krishnamurthy built the computer using locally purchased potentiometers and resistors.

The computer was named "Lilavati," after the daughter of Bhaskara, a twelfth-century Indian mathematician. Bhaskara wrote a famous treatise in mathematics called "Siddhantha Siromani" in 1150 AD; one of its four parts that dealt with arithmetic was also called "Lilavati." Krishnamurthy's computer solved linear simultaneous equations as expected, without the use of pencil or paper. Even though the digito-analog computer itself was original and unique but primitive for its time, the theoretical computing issues that Krishnamurthy and Ramachandran developed were accepted for publication by the *Quarterly Journal of Applied Mathematics*, an Oxford-based prestigious journal on the subject. Krishnamurthy is currently a professor in the Computer Sciences Laboratory of the Research School of Information Sciences and Engineering at the Australian National University in Canberra.

At any given time there were at least a dozen graduate students working on different problems in Ramachandran's laboratory. Some of them were supported by research fellowships of 56 or 80 rupees per month, provided by Madras University. Some had Government of India scholarships of 200 rupees a month, there were a few who had University Grants Commission or CSIR (Council of Scientific and Industrial Research) scholarships of 250 rupees per month. After obtaining their doctorate degrees, Srinivasan and Sasisekharan were hired as lecturers in the department.

It was not always easy for graduate students to meet and discuss their research projects with Ramachandran, as he was always busy working on his own projects. Most of the time he was in his office reading or writing extensively. But senior graduate students always helped their juniors with problems in crystallography, so it was not necessary for them to see "the Professor." Very often he would spend long hours talking and discussing with some chosen student who was working on a problem of particular interest to him or who had obtained a result that excited him. Ramakrishnan for example would spend hours talking to Ramachandran on results of his calculations on the stereochemistry of polypeptide chains. When such discussions took place no other student could get a chance to see Ramachandran.

There was a certain aura surrounding the Professor. New students in the department were simply afraid to see him alone in his office. Ramachandran was known to be very temperamental, easily irritable;

sometimes in a good mood, very often not. His personal secretary, Mr. K. P. Ramachandran was one of the first persons to see him each morning. Professor Ramachandran would dictate the official letters he had to write in his capacity as head of the department. KP, as he was usually called, would transmit the Professor's mood to the students in his laboratory and they then decided if they had the courage to enter his office to ask any questions. Ramachandran disliked the routine administrative chores, but at least in the beginning there was no one else who could do such things as writing letters to the Vice Chancellor or to other administrators in the university and government funding agencies.

The only time when Ramachandran appeared relaxed was when he and the rest of the department attended farewell parties for colleagues who left for England or the United States for post-doctoral work; Chandrasekharan, Kartha, Raman, Krishnamurthy, Sasisekharan, Thathachary, and others all left India for further training. Even at these parties, usually held in local restaurants the atmosphere could be rather tense once Ramachandran arrived. There was no reason for any tension, because Ramachandran was gracious and could easily carry on a conversation on any subject. But it seemed that, in general, Ramachandran controlled the conversation, and the discussions were never trivial. One reason for the assumed tension was that all present were former or current students and it was an Indian tradition to maintain a respectable distance between a teacher and a student. There was also a sense of awe and respect for the individual who everyone conceded was intellectually head and shoulders above the rest of the company.

12. First International Symposium in Madras

Twelve years after he returned from Cambridge, Ramachandran made his next foreign trip, spending three months in Germany, a week in Stockholm, and two weeks in England. He wrote to several people and arranged to visit their laboratories. Many of them had not heard of Ramachandran or Madras. The contacts he established during this trip and his scientific accomplishments enabled him to successfully organize an international symposium in Madras in January 1963.

He had invited Sir Lawrence Bragg to visit Madras. Bragg was the director of the Cavendish Laboratory in Cambridge when Ramachandran was working for his doctorate degree nearly fifteen years earlier. Bragg had moved from Cambridge to the Royal Institution of Great Britain in London, where as director he was gathering a group of young crystallographers to work on protein structures, just as he had done earlier in Cambridge. Initially, Bragg agreed to come to India with his wife. The symposium was arranged around his visit in order to give an opportunity for the crystallographers in India to meet and listen to Bragg. Unfortunately, at the last minute Bragg was unable to attend the symposium due to some unexpected health problems. In his place he sent David Phillips (now Lord Phillips of Ellesmere) who had just moved from the Medical Research Council Laboratory in Cambridge to the Royal Institution.

It took an enormous amount of hard work to organize a symposium; everyone in the department was totally involved in some aspect of the symposium. There was no precedent for such an event at Madras University. The lectures had to be planned and lecturers for each session had to be chosen. Appropriate personalized invitations had to be sent to each scientist and tracked. Travel and lodging arrangements had to be made for the visitors from Australia, England, Europe, Israel, Japan, the Soviet Union and the United States. Now there are private organizations that can handle these arrangements. But Ramachandran had to do all of this at a time when there were only two large Western-style hotels in Madras, Hotel Oceanic and Hotel Connemara. There was no large air-conditioned auditorium in Madras University; perhaps it was not necessary in the winter-like weather in January. However, to reduce disturbance from outside noise in the lecture rooms, special air-conditioning units were installed in the lecture halls of the Madras University buildings where the meetings were to be held.

In Ramachandran's own words: "The 1963 symposium was the first of its kind in India, for the number of foreign delegates who attended the meeting. There were three Nobel laureates from outside India, Severo Ochoa, Maurice Wilkins, and Stanford Moore. Our own Raman, as the fourth Nobel laureate, added luster and color to the distinguished list. Sir Lawrence Bragg, who was supposed to come, withdrew at the very last minute due to illness. Instead he designated David Phillips to attend the meeting, who according to Bragg was "the most senior among our junior colleagues." Three years later David Phillips led the group of scientists who determined the structure of lysozyme, the first enzyme structure to be determined.

According to Ramachandran,

> There was no money available to finance the symposium. I had a good friend in Dr. Ernest C. Watson, who was previously Dean of Faculty, at Caltech, Pasadena. Fortunately for me he was the science attaché to the U.S. embassy in New Delhi and we became good friends. When I had financial difficulty, I wrote to him and asked for assistance. He called me and asked me to send him a copy of the tentative program, a list of all the invited speakers, their qualifications, and where in the United States they were coming from. He wrote to the NIH and NSF endorsing our proposal with his strong approval and highly recommending support. We did not get any big block grant, instead the U.S. government took care of boarding and lodging and travel expenses of all the scientists coming from the United States.
>
> Wolfie Traub and Ephraim Katchalski (later to become the President of Israel, Ephraim Katzir) were both coming from Israel, but they could not get visas, as India did not have diplomatic relations with the government of Israel. Then Rajam's brother, Mr. T. S. Sankaran, who was a senior officer in the Indian Administrative Service, helped us to get visas for them. Sir A. L. Mudaliar, the Vice Chancellor of Madras University, wrote to the University Grants Commission and obtained financial support. The University of Madras itself did not have too much money and could not help us out too much, but I think we got money from the UGC for some of the expenses of the meeting. Thyagaraja

> Rao and several other graduate students in the department prepared a brochure for the conference and collected money from various advertisers in Madras.

The conference began with a keynote address by Professor Sir C. V. Raman, followed by scientific presentations by most of the participants. There was lively discussion after every paper. The Academic Press published the proceedings of the Madras Symposium in two separate volumes in 1963. There was of course a banquet for all the participants, at which the guests were treated to delicious Indian cuisine followed by a classical music concert by the famous M. S. Subbulakshmi.

Foreign guests did not come to India just to attend the symposium; many wanted to see other tourist attractions in India, and such visits had to be arranged by the organizers of the symposium. Language was another major problem for outside visitors. Tamil is the language of Madras, even though most residents in Madras understood and could communicate in English. Ramachandran's students found themselves working as scientists, travel agents, tour guides, and translators, all at the same time. Almost all visitors were very highly impressed by Indian hospitality, the intellectual and scientific content of the symposium, and the mystique of the Indian subcontinent.

A winter School on Advanced Methods of Crystallography was organized at Madras University following the International Symposium. Many of the leading scientists who attended the symposium were requested to deliver a series of three lectures in the winter school, which was spread over six days. The lectures dealt with various aspects of crystallographic research, methods of structure determination, study of crystal imperfections, disorder and thermal vibrations and their effects on X-ray scattering, theory of neutron diffraction, and application of group theory to the study of various crystal properties, among other topics. The lectures delivered in the Winter School were also published by the Academic Press.

The 1963 symposium and winter school set an admirable precedent for a number of similar symposia arranged regularly in Madras, usually around the visit of some famous foreign scientist. A second such symposium was held in 1967 to coincide with the visit of Linus Pauling. Dorothy Crowfoot Hodgkin was another distinguished visitor to Ramachandran's department in later years and a symposium was arranged during her visit too. Such events provided an excellent opportunity for students and local scientists in related fields to meet visiting dignitaries.

Students about to complete their doctoral theses used these visits by the foreign scientists to arrange postdoctoral fellowships for themselves in laboratories around the world. Once the students left India, most of them settled permanently outside India, resulting in an unfortunate "brain drain". Thanks to Ramachandran and his coworkers, Madras had established itself as a center for advanced research in biophysics, and scientists from other universities and institutions in India considered it a great privilege to participate in the Madras symposia.

13. Second International Symposium in Madras

Elated with the success of the first International Symposium in January 1963, and the development of a hard sphere model for finding the allowed conformations of a polypeptide chain, Ramachandran decided to organize yet another International Symposium on Conformation of Biopolymers in January of 1968. By then, the University of Madras had endowed the Raman Visiting Professorship of Physics to enable distinguished scientists from England or the United States to spend a few weeks in Madras. The first Raman Professor was Sir Lawrence Bragg, who had visited India in 1965 with his wife as guests of Ramachandran and the University of Madras. At that time, they were treated royally, visited several laboratories throughout the country, gave a series of lectures, and also visited numerous attractions in various parts of India.

In 1967, Ramachandran invited Linus Pauling to come to India as the Raman Professor of Physics and also decided to organize a symposium around this visit. The International Union of Pure and Applied Biophysics cosponsored the symposium. There was a very distinguished organizing Committee that included Chris Anfinsen, Bill Harrington, Fred Richards, Harold Scheraga, and Ramachandran. Having organized one international symposium, the second one was much easier, receiving generous financial support from the Indian government through the University Grants Commission, Council of Scientific and Industrial Research, and the Atomic Energy Commission. Ramachandran was an internationally known scientist and the University of Madras and the government of India readily extended their support. A large number of scientists, both from within and outside India attended the four-day symposium.

In his Presidential Address, Professor Linus Pauling traced the history of the structure of proteins, both in crystalline and fibrous forms, his own work on the discovery of the alpha helix, and his work on the structure of collagen. In the last part of his lecture he acknowledged: "It turned out that Professor Corey and I did not get to make our second guess [about the structure of collagen]. In 1955, Professor Ramachandran and his coworker G. Kartha described the striking triple-helical structure of collagen that is now generally accepted as being correct. Although I may have some feeling of regret that Professor Corey and I did not succeed in making our second guess, which I trust would have turned out to be the right one, I may point out that the problem was a very difficult one, and that Professor

Ramachandran and his coworkers deserve great credit for their successful attack on it, and their continuing vigorous effort in the solution of the many difficult problems in the field of protein structure and other aspects of structural chemistry to which they have devoted themselves for many years."

Papers presented at the 1968 symposium covered a wide range of topics including X-ray diffraction and stereochemical studies of proteins and polypeptides, optical rotation studies, chemical studies, and statistical mechanical studies. There were also sessions on studies of collagen and related polypeptides, nucleic acids, and polysaccharides. Some of the pioneers in the field of polypeptide conformations like Harold Scheraga, Paul Flory, George Nemethy, John Schellman, and Elkan Blout were present at this symposium.

Sasisekharan and Ramachandran presented a paper describing their successful hard sphere approach to the study of the conformations of polynucleotides and nucleic acids. Unlike the case of polypeptides, the experimental measurements of the dimensions of nucleotide monomers are meager which makes it difficult to choose proper values for the relevant parameters. Moreover, the nucleotide unit is not as rigid as a peptide unit and there are a large number of possible free rotations in the nucleotide structure. In spite of this, the authors showed an enormous restriction in possible orientations in polynucleotides. In addition, Ramachandran was also an author in a paper on the conformational studies on the polysaccharide amylose, a polymer of glucose. In this paper the authors used potential energy calculations of non-bonded interactions to deduce the structure of amylose which they showed was in good agreement with the structure derived from experimental data.

Ramachandran was an author in all five papers presented by different people working in his department in Madras. Clearly it was one of the most important meetings in Ramachandran's scientific career, because it not only placed him as one the undisputed leaders in this field, it also raised the prestige of his department in Madras to a totally different level. Once again, the Academic Press published the symposium proceedings in two volumes.

14. Conflicts in Madras

Among students who obtained their doctorate degrees under Ramachandran's direct supervision and went as fellows to laboratories in England and the United States, Gopinath Kartha occupies a very singular place and deserves special mention for several reasons. As the first associate of Ramachandran, he was a key player in establishing the Madras department. He was Ramachandran's collaborator on the determination of the structure of collagen. Kartha was also the first associate of Ramachandran to settle in the United States. He started at the Brooklyn Polytechnic Institute in the Laboratory of Professor David Harker, the well-known American crystallographer. Harker moved to the Rosewell Park Memorial Institute in Buffalo, New York, and Kartha moved with him. He spent over thirty years in the Crystallographic Research Center of the Rosewell Park Memorial Institute. A pioneering protein crystallographer, Kartha started the very first X-ray crystal structure analysis of the protein ribonuclease in the United States. He completed the structure and shared the honor with Frederick Richards and Harold Wyckoff of Yale University. Kartha continued his work on several interesting crystallographic problems. Unfortunately, he suffered a series of heart attacks and eventually died in the prime of his life.

In Ramachandran's words: "Kartha was the best postdoc I ever had. After he left for the United States, and started the ribonuclease investigation, he was very frustrated. It was Bellow who had crystallized the protein, and David Harker wanted to give all credit to Bellow. But it was Kartha who was doing all the work required to solve the structure. Kartha got so frustrated that he wanted to simply give away all the data to anyone who wanted it, and slowly lost interest in that problem. Kartha never liked publishing papers. He solved the crystal structure of morellin, an organic compound we obtained from the National Chemical Laboratory in Poona, but he never published the result. Similarly, Ephraim Katchalski sent me a tripeptide Pro-Pro-Pro; Sasisekharan and Ramakrishnan solved the structure by energy minimization, and I sent the material to Kartha who solved it by X-ray diffraction, and he never published it either."

Ramachandran made a long visit overseas in 1966. It was his first trip outside India since his student days. He went to the Department of Biophysics at the University of Michigan at Ann Arbor to be a visiting professor at the invitation of Professors Onclay and Krimm. While in

Ann Arbor, he asked Professor John Edsall of Harvard if he could arrange a part time research appointment for him at Harvard every summer. Edsall said they did not have such a provision, and instead suggested the University of Chicago. Professor Robert Langridge who was then in Chicago helped to fulfill Ramachandran's wish, but then he left for Princeton immediately afterwards. Thus began a long-term association between Ramachandran and the University of Chicago Department of Biophysics, where he was a part-time professor during the period between 1967 and 1978. He applied for and got an NIH research grant for working in Chicago and to hire a full time post doctoral research associate, who was stationed in Chicago to work on his research project even when he was not there. Ramachandran usually employed one of his students from Madras for periods of two to three years.

Ramachandran was expected to visit Chicago every summer between May and August as part his appointment. Sir A. L. Mudaliar, the Vice Chancellor of the Madras University, had no objections to his annual trips, and considered it a great honor for the University to have one of its faculty members hold a joint appointment with the prestigious University of Chicago. He was happy to grant Ramachandran leave of absence. This was to change after Mudaliar left the university in 1968 and Mr. Sundaravadivelu became the new vice chancellor. Surprisingly, he refused permission to continue the practice even though Ramachandran's visits to Chicago imposed no financial obligations on the University of Madras.

This was one of the earliest signs of conflict between Ramachandran and the new administrators of the University of Madras. Sir A. L. Mudaliar was a great educator and had maintained a very high standard of education at a university which enjoyed an exalted reputation. This was achieved by hiring eminent scientists as department heads, keeping them happy by providing a highly intellectual environment, and allowing them to conduct research without interference and to train young scientists in their respective fields of research. In addition to Ramachandran there was Professor Alladi Ramakrishnan in the theoretical physics department and Professor T. S. Sadasivan, who had built one of the finest botany departments in the whole country at Madras. Then there was Professor P. S. Sarma in the biochemistry department, and Professor S. Swaminathan in the organic chemistry department. When any of these professors identified a good scientist whom they wanted to hire in their departments, all they had to do was to convince Mudaliar and a new faculty position would be created immediately.

Several colleges affiliated with the University of Madras enjoyed full autonomy in administration and selection of faculty. The University science departments were focused on postgraduate education and research and their primary mission was to train scientists to teach and do research. A committee consisting of prominent elected educators from the State of Madras called the "University Syndicate" determined the administrative policies of the University. Many of its members were professors from affiliated colleges. Ramachandran's father was a member of the syndicate when he was the principal of the Maharajah's College in Ernakulam. A Registrar was in charge of the routine day-to-day administration of the University.

By all accounts Ramachandran was a superstar in the University; Mudaliar knew it and did everything within his power to keep him happy. Mudaliar was quite aware that Ramachandran had conducted science of the very highest caliber and had received international recognition for it. There were frequent rumors about a Nobel Prize for Ramachandran and people in the department used to gloat that he was "frequently knocking at the door of Nobel Prize." He was already a recipient of the prestigious Jawaharlal Nehru Fellowship at the University. The University Grants Commission, India's major funding agency for higher education, made large awards of grant money to Ramachandran's department for the purchase of equipment and fellowships to train graduate students in biophysics. The department was named the "Center for Advanced Study in Biophysics and Crystallography." The Department of Botany under Professor Sadasivan was the only other department in Madras University that was similarly designated as a Center for Advanced Study.

One instance of Mudaliar's continued support is reflected in Ramachandran's words: "I wanted a computer for the department, Mudaliar made a very strong recommendation to the UGC and the UNESCO. Malcolm Adisheshayya, who later became a Vice Chancellor of the University of Madras for a very short time, was a deputy director of the UNESCO and he helped to arrange funds for a computer. We acquired an IBM 1130, which is probably not as powerful as many current personal computers, but it helped us at that time with our research."

Mudaliar actually protected Ramachandran from most routine bureaucratic and administrative assignments required of a University Professor by the Syndicate. Mudaliar simply allowed Ramachandran to concentrate on his research. In fact R. Srinivasan, who was by then a professor in the department, managed the routine administrative duties of the department. Alladi Ramakrishnan had also been promoted as a professor of theoretical physics, first at the Madurai Campus of the University of Madras. Ramachandran had absolutely nothing whatsoever to do with Alladi Ramakrishnan's transactions with the university, even though he was originally hired to be part of the Department of Physics in which Ramachandran was designated the head of the department. In fact, Alladi Ramakrishnan was already in the process of building a separate Institute of Mathematical Physics in Madras using his reputation as a leading theoretical physicist and a member of the famous Alladi family.

All this patronage and support disappeared when Mudaliar retired as Vice Chancellor and Sundaravadivelu replaced him. By all accounts Sundaravadivelu was an antithesis of Mudaliar. He was director of public education in the State Education Department before he became the Vice Chancellor of a major university and certainly did not seem to understand the subtleties of research or higher education. It was also generally believed that he had a dislike toward the Brahmin caste, that in his opinion, had dominated all aspects of life in Madras, particularly in the field of education. Ramachandran and several other Madras University professors belonged to the Brahmin caste.

Madras, now called "Tamil Nadu," enjoyed an ancient rich tradition and culture dating back to several hundred years. It also had some of the worst caste relations in South India. Hatred of the Brahmin caste was highly visible in Tamil Nadu. Brahmins, who originally belonged to the priestly class, were well educated and occupied many senior administrative positions in the state and federal governments. This situation fostered a revolutionary political organization called "Dravida Kazagam," a party of Dravidians whose goal was to improve the destiny of non-Brahmins in all walks of life. Historically, South Indians were of Dravidian decent while the North Indians were considered to be of Aryan decent. There has, of course, been considerable amount of intermixing of the two classes over many generations.

Dravida Kazagam was very active politically and turned the hatred toward the Brahmin class into legislative advantage, setting in place a generous quota system for non-Brahmins in higher education and government jobs. The general impression was that there was a total disregard for merit and Brahmins had a very hard time obtaining admission to medical and engineering colleges. There was even sporadic violence against members of the Brahmin community. It was under these circumstances that Ramachandran was running the physics department in the university under Mr. Sundaravadivelu. Unfortunately, even after nearly three decades, the situation has not changed very much in Tamil Nadu and the apparent discrimination against Brahmins continues to this day.

According to Ramachandran, "Sundaravadivelu did not appreciate that our department was better than several other departments in the university. For instance, I was having some collaboration with one Dr. Natarajan of the biology department. Sundaravadivelu did not like it, he felt that there should be no collaboration between departments, biology should not be done in physics department or vice versa [sic]. In general there was a very hostile atmosphere."

There were several other instances of "hostility" between Ramachandran and Sundaravadivelu. There was a vacancy for a Reader's job in the Center for Advanced Study in Biophysics and an informal offer was made during Mudaliar's regime to one of Ramachandran's former students who had done some years of postdoctoral research in North America. The new Vice Chancellor reneged on that offer and Ramachandran could do nothing about it. Ramachandran decided to hire him instead as a pool officer of the government's Council of Scientific and Industrial Research. The CSIR created this position to help resettle Indian scientists returning from postdoctoral training abroad. The scientists hired could remain in the pool until they found more permanent jobs in India. Sundaravadivelu apparently invoked some archaic rule that no department could have more than one scientific pool officer at any given time and Ramachandran's department already had one and he blocked the appointment.

On another occasion, without prior consultation with Ramachandran or Srinivasan who had replaced Ramachandran as the department head, Sundaravadivelu hired a non-Brahmin as a computer programmer and sent him to work in their department. Not only was there no need for a new programmer, it also was alleged that this individual had no suitable qualifications for that position.

Ramachandran refused to accept the programmer and did not allow him to enter the department, resulting in yet another unpleasant confrontation between him and the vice chancellor.

It was in this context that Sundaravadivelu refused to grant Ramachandran leave of absence to go to Chicago as a visiting professor every summer. In fact, Ramachandran had to obtain permission from the registrar's office before he could take even half a day's leave. In one instance, Ramachandran wrote to the Registrar on 4 August, 1967: "As I have to perform my father's annual ceremony [a religious observance performed on the death anniversary] I will not be able to attend the department during the forenoon of Saturday, 5 August, 1967. I request you to grant me half a day's casual leave." On 13 September, 1967, more than five weeks after the event, a secretary from the Office of the Registrar sent a routine form letter with his initials granting the professor casual leave for 5 August! Such was the bureaucracy in the halls of the University of Madras.

It is ironic that an individual of Ramachandran's stature had to apply for a half-day's casual leave from the Registrar of the university. That same year Ramachandran received a letter from the Nobel Committee in Stockholm asking him to nominate a scientist for the Nobel Prize in Physics for 1967. He replied that he was more familiar with the most recent advances in Chemistry or Medicine and that he would be happy to nominate a scientist for a Nobel Prize in those fields. He nominated H. G. Khorana for the Nobel Prize in Chemistry.

All these events were too much to take for Ramachandran, and he decided to return to Bangalore to start a new life.

15. Bangalore Revisited

In 1970, Ramachandran resigned from the University of Madras and moved to the Indian Institute of Science in Bangalore, the same place where he had started his scientific career. Professor Satish Dhawan, a well-known space research scientist and an aeronautical engineer, was the director of the institute at that time. He invited Ramachandran to the institute and promised full support.

In Professor Dhawan's words: "Professor Ramachandran's capabilities were simply great, setting aside his physical problems. He came here because he was unhappy in Madras. In fact, I had requested him to start a seminar series in molecular biology in the Institute, with the help of various divisional chairmen. . . . I casually told him that he should come to the institute if he was unhappy in Madras; the next thing I know he knocked on the door of my office and said he would come. We made an offer that he could not refuse and so he came to Bangalore. His job was to start a molecular biophysics group. In fact before he came here, I went to each chairman in the institute and asked them frankly: 'Did they like to collaborate with him, did they welcome him or did they dread him?' Everyone was happy that he was coming and they welcomed him. He brought some of his own people, V. S. R. Rao, V. Sasisekharan, C. Ramakrishnan, and others."

Thus began another saga, in a tale of two cities, in the life of Ramachandran. Though Ramachandran resigned from Madras University in 1970 and with a clear mandate to start a new department of molecular biophysics at the Indian Institute of science, he immediately left for Chicago for one year. There he began recruiting some faculty members from the United States for his new department. He officially started the new department in 1971.

Originally a few members went with Ramachandran from Madras and later even more joined him in Bangalore. A critical mass was attained very quickly, the faculty who joined Ramachandran were very excited at the prospect of a new department under the leadership of the world renowned Ramachandran. V. S. Ananthanarayanan was a physical chemist, who got his degree in physical chemistry with Professor Santhappa from the University of Madras, and did postdoctoral work in Professor Harold Scheraga's laboratory at Cornell University. He met with Ramachandran in Chicago in 1970 and was immediately recruited to be one of the first members of the new department in

Bangalore. His interests were in optical hydrodynamics and optical rotatory dispersion. C. Ramakrishnan and V. Sasisekharan, who were once Ramachandran's students, were working on the confórmations of polypeptide structures and V. S. R. Rao was using the same principles to study the conformations of polysaccharides. All three were colleagues of Ramachandran in Madras and joined the department in Bangalore within the first year.

K. R. K. Easwaran, M. Vijayan and P. Balaram also joined the Molecular Biophysics Unit, at various times afterwards. Vijayan was an X-ray crystallographer who obtained his doctorate from the Department of Physics in the Institute and did postdoctoral research in the laboratory of Professor Dorothy Hodgkins in Oxford, England. A bioorganic chemist, Balaram who had obtained his doctorate in the United States and did postdoctoral research in Woodward's laboratory at Harvard. R. Chandrasekaran, a former graduate student and a postdoctoral fellow in Ramachandran's laboratory in Chicago, also joined the Molecular Biophysics Unit. He remained in Bangalore for only a couple of years, and left because of personal problems relating to bureaucracy and living conditions in India. Specifically, the same denial of leave of absence that led Ramachandran to move from Madras to Bangalore repeated itself in case of Chandrasekaran. He took a permanent job in the United States where he is a professor of structural biochemistry at Purdue University in Lafayette, Indiana. His primary area of research is X-ray fiber diffraction of non-crystalline biopolymers.

Starting a new department in Bangalore was not smooth sailing for Ramachandran, in spite of the institute being a leading research institution in India. First of all, there was no benefactor like Sir A. L. Mudaliar. Dhawan, who was the director of the Institute at that time, had too many commitments. After the unexpected death of one of India's leading scientists, and chairman of the Indian Space Research Organization, Vikram Sarabhai, Dhawan had to take on that additional assignment. He was also a senior member of a panel that was investigating a number of plane crashes in India involving Soviet-built AVRO planes. These activities kept Dhawan extremely busy and he was often away from Bangalore. Whenever he came to the institute, his students greeted him with a sign saying, "Nice to see you Dr. Dhawan." As someone starting a new department, Ramachandran needed a lot of help in obtaining funds to buy new equipment for the different investigators.

Ramachandran applied to the University Grants Commission (UGC) for an Advanced Center for Biophysics in Bangalore, similar to the one he had in Madras. The biology section of the UGC said that his request was in the domain of the physics section, but the physics section said that it was in biology's domain. In another incredible example of Government bureaucracy, they finally agreed that since he was instrumental in starting a Center for Advanced Studies in Madras and left it to go to Bangalore, he should not get a second center.

In general the Indian Institute of Science had a reputation that each director looked after his own department. This was not all that bad since directors were chosen from different departments of the Institute at different times. Raman took care of physics and the director who succeeded him fostered the engineering departments. Director Bhagavantham's period did not see either a new department or any new innovations. Dhawan, an aeronautical engineer, was partial to the needs of that department and encouraged space research. Director C. N. R. Rao developed research in structural chemistry. Under current Director Padmanabhan, biological sciences, biochemistry, and molecular biology are being developed.

While in Madras, Ramachandran had a research grant from the National Institutes of Health in the United States. Luckily, this grant was transferred to Bangalore, and he could use the funds for purchasing small equipment and chemicals, however, there were not enough funds for more sophisticated equipment or a computer. Much of the equipment and chemical supplies needed to do research had to be imported from outside India and this usually required payment in American dollars or British pounds. The government of India kept strict control on the release of foreign exchange and Ramachandran's research grant from the NIH was extremely valuable in providing the necessary foreign currency.

16. Year in Chicago

Ramachandran had still his part-time appointment in the Department of Biophysics at the University of Chicago and he was expected to spend the summer there from May to August. For two successive years, in the midst of his move from Madras to Bangalore, he could not fulfill this obligation. Therefore he decided to spend one full year from April 1970 to June 1971 in Chicago. He expressed his desire to teach some courses in Chicago, but it was not approved. Consequently he devoted all his attention to research and it proved to be an extremely fruitful year. He succeeded in getting two postdoctoral positions for his laboratory: R. Chandrasekharan studied peptide and protein conformations and A. V. Lakshminarayanan worked in the field of X-ray tomography.

In an extraordinary move, the National Science Foundation awarded Ramachandran a research grant for two years on very short notice. An urgent application was sent by Ramachandran to Dr. McElroy, the director of National Science Foundation, who got it evaluated immediately and asked Ramachandran to present an outline of his project in the form of a seminar in Washington, D.C. Within two weeks the grant was approved. The administrators at the University of Chicago were absolutely delighted about this development because the biophysics department was paying part of the expenses of Ramachandran's postdoctoral fellow, which could now be paid from the National Science Foundation award.

During this period, Ramachandran made an important contribution in the field of biophysics dealing with the three-dimensional reconstruction of an object from two-dimensional shadowgraphs of a number of its slices. This technique has several practical applications. Structures of microorganisms, such as bacteria or viruses, are often studied using electron microscopes. Each electron micrograph provides a two dimensional projection of a three-dimensional object. By rotating the object around a single axis it is possible to generate several electron micrographs or several projections of the object. These projections are mathematically combined to produce slices of the three dimensional image of the object. Ramachandran and A. V. Lakshminarayanan, a postdoctoral fellow and one of his former students from Madras, developed a new method and worked out the theory for such a reconstruction. They called it "Computerized Axial

Tomography" or CAT.

This project actually resulted from a meeting Ramachandran had with Aaron Klug in Cambridge, England. Klug had done pioneering work on image reconstruction of electron micrographs of virus particles. These were done in three dimensions, while Ramachandran used Fourier transforms of the projections, meaning that the calculations were done in two dimensions. This resulted in quicker and easier computations.

Ramachandran sent the first paper on this topic to C. V. Raman in October 1970 for publication in the *Proceedings of the Indian Academy of Sciences*. Raman accepted the paper a few weeks before he died in November of 1970. Ramachandran continued this work in Chicago, where computing facilities were much better. Professor S. Chandrasekhar, the Nobel astrophysicist from the University of Chicago, communicated a second paper on the subject in 1971 to the *Proceedings of the National Academy of Sciences*, in the United States.

This paper is purely mathematical and highly theoretical, containing many complicated equations on Fourier transforms and convolutions. The most convenient mathematical technique for reconstructing a structure of a three-dimensional object using data generated from transmission photographs is by way of Fourier transforms. These trans-

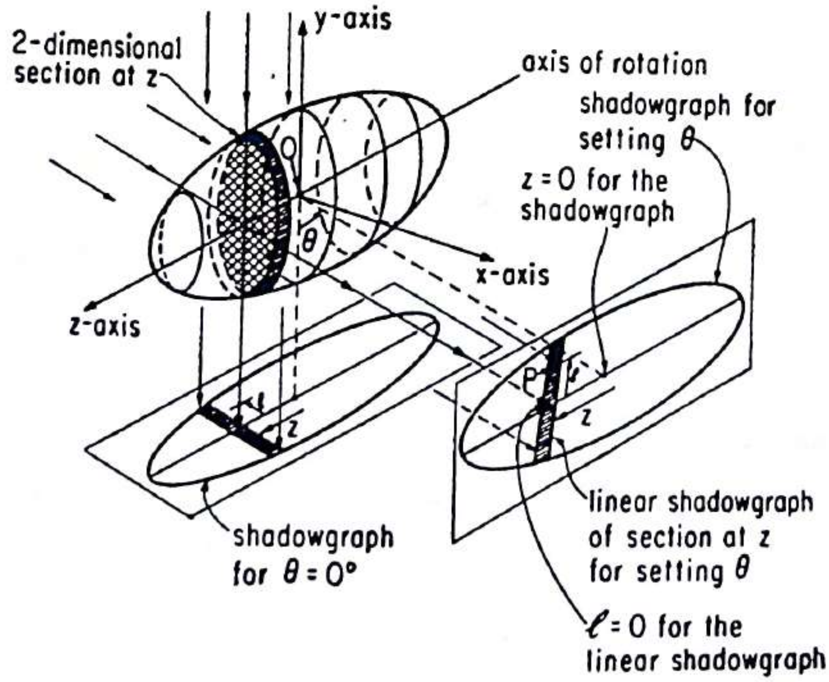

y-axis
2-dimensional section at z
axis of rotation
shadowgraph for setting θ
z = 0 for the shadowgraph
θ
x-axis
z-axis
ℓ
z
P
ℓ
z
shadowgraph for θ = 0°
linear shadowgraph of section at z for setting θ
ℓ = 0 for the linear shadowgraph

Figure 14: Formation of planar shadowgraphs of a three dimensional object at different angular settings theta of the beam. (The linear shadowgraphs of the section at z and the origin for the measurement of 1 in it are also shown).

mission photographs are usually taken at various orientations of the object and are called "shadowgraphs". Klug and Derosier first published this method in 1968 and used it to reconstruct virus structures from two-dimensional electron micrographs.

The data in two-dimensional shadowgraphs is transformed into its Fourier space in two dimensions, collated to obtain a three-dimensional Fourier transform of the object, which is then back-transformed to give the original object in three dimensions. It is well known that the Fourier transform of the convolution of two functions is the product of the Fourier transforms of the individual functions. Therefore, any reconstruction technique based on Fourier transforms is capable of being rewritten in a new language such that it is converted to a set of formulae involving only convolutions.

In Ramachandran's method, three-dimensional Fourier analysis is avoided and only one- and two-dimensional syntheses are used, thereby reducing the computational times involved. In this method the object is rotated about an axis and shadowgraphs are obtained by having a parallel beam of radiation coming at right angles to the axis of rotation. Transmission photographs are taken at different rotational settings of the object about its axis. This is equivalent to keeping the object fixed and rotating the radiation source about the same axis. Using only convolutions they reconstructed the image in three dimensions. Because the formulae involve only summations over one variable at a time, the convolution method is much faster than the two dimensional reconstruction with Fourier transforms which requires double summations. The relative increase in speed is even larger when greater resolution is required. The required number of shadowgraphs is also reduced, along with the computing time required for the reconstruction process. This is the basic principle of Magnetic Resonance Imaging, or MRI, now used so successfully in clinical diagnosis. The construction of a practical CAT scan model was finally completed three or four years later in England and the scientists involved in the work received the Nobel Prize in 1979.

Professor Ochoa asked Ramachandran to apply for a research grant to the Jane Coffin Childs Memorial Fund, a highly prestigious funding agency that supports cancer research. The grant application was to analyze radiography from shadows of tumors, and Ramachandran was awarded $15,000 for initial studies on the project. Ramachandran wanted to design and construct a practical device, but unfortunately there was no suitable engineering department to help him at the

University of Chicago. Also, the biophysics department had neither the expertise nor the interest in constructing the instrument.

Ramachandran continued his research on protein structures and peptide conformations. R. Chandrasekaran, a postdoctoral fellow in Chicago, worked with him on conformations of peptides with alternating sequences of L and D amino acids. Such sequences are biologically significant because they are often found in important peptides participating in transport of ions across membranes or in antibiotics. Almost all antibiotics contain D amino acid residues and structural studies of such peptides were important in understanding their biological activity.

While in Chicago, Ramachandran interviewed Dr. Balaram for a job in the new Molecular Biophysics Unit in Bangalore. Balaram was doing postdoctoral research in Woodward's laboratory in Harvard at the time. He was asked to go to Chicago to meet Ramachandran in the University campus. As Dr. Balaram recalls: "First thing he asked me was if I knew about the structure of collagen. Being an organic chemist, I had not heard of collagen and so I said I did not know about it. I think he was annoyed and disappointed at me but went on to talk about some one and two hydrogen bonded structures and asked me if NOE [Nuclear Overhauser Effect] or NMR [Nuclear Magnetic Resonance] would distinguish between the two structures, I said no to that. Then there was a long silence. K. P. Sarathy, his postdoctoral fellow joined us, again there was a long silence. As I remember it, we marched off to lunch to some canteen, there was a strange silence, and then he abruptly said he was busy and walked away. That was that."

Woodward usually does not write too much about other people, but when he actually does he tends to go overboard. Apparently he sent a long cable to Ramachandran about Balaram which eventually reached the selection committee and Balaram was immediately hired as a lecturer in the Molecular Biophysics Unit. Ramachandran believes that this was one of the best selections he made for the unit.

There was a down side to Ramachandran's frequent visits to the United States and to the University of Chicago—he always returned frustrated and depressed at his inability to do the kind of research in India that he could do abroad. Computing facilities were so primitive in Bangalore that his students and postdoctoral fellows had to wait for long hours to get on a computer. Often other biophysicists in the United States were working on problems similar to what he was working on, but there was no way he could compete with them.

17. Turmoil in Bangalore

Ramachandran returned from Chicago in 1971 to continue the expansion of the Molecular Biophysics Unit at the Institute. He recruited new faculty members and planned an educational curriculum for postgraduate and doctorate programs. V. S. Ananthanarayanan (VSA) and K. R. K. Easwaran (KRKE) were the first two members recruited as senior research fellows with the promise of a faculty position as soon as one was created. Both were appointed as assistant professors soon afterwards and VSA took over the responsibilities of running the department, attending chairmen's meetings in Ramachandran's place even at these early stages. Ramachandran and his NIH grant for research in India provided valuable foreign exchange for purchase of chemicals and equipment, including a new circular dichroism machine. But there was no separate building for molecular biophysics and no real laboratory space for any of the faculty. VSA and KRKE conducted their experiments in the organic chemistry, biochemistry, or chemical engineering departments.

At the same time, Ramachandran was busy initiating a Molecular Biology Discussion Group that included members from the departments of biochemistry, microbiology, chemistry and physics. The participants met occasionally to discuss research topics of mutual interest.

By 1974, there were nine faculty members in the Molecular Biophysics Unit (MBU)—Ramachandran, Sasisekharan, V. S. R. Rao, C. Ramakrishnan, KRKE, VSA, P. Balaram, M. Vijayan, and R. Chandrasekaran. It was jokingly referred to as the "Madras Brahmin Unit" (MBU), even though not all members were Madras Brahmins, and race or caste was simply not on anyone's mind. The faculty was young, ambitious, and quite enthusiastic about being part of a team under the leadership of someone as famous as Ramachandran.

Ramachandran welcomed the entry of Sasisekharan to Bangalore probably because he had known him for the longest period of time. Ramachandran never liked routine administrative tasks; he either thought them a waste of his time or felt that he was unable and unqualified to contribute and achieve anything significant in administrative meetings. He therefore requested that Sasisekharan be made chairman of the department. Nevertheless, Ramachandran had his own strong views and opinions about matters concerning the administration of the department and he did not hesitate to make them known to

Sasisekharan or to anyone else. Much to the displeasure of everyone in the department, he would often try to impose his wishes through Sasisekharan in the department's faculty meetings.

Ashok Kolaskar, Manju Bansal, and Alop Mitra were some of the first students of Ramachandran in Bangalore. Manju Bansal was his only female student. Ramachandran would interview all students who were admitted into the graduate program, rank them according to their merits, and usually selected the top ones in the list to work with him. The students considered it a great honor to have been selected to work with Ramachandran, much to the dismay of some other members of the department.

Raj Bhatnagar, an organic chemist from San Francisco was on a sabbatical leave at the institute. He provided a number of collagen-like synthetic di and tripeptides for Ramachandran to study their physical chemistry and X-ray diffraction. But there was no X-ray generator at that time in the unit. The students had to take their crystals to the X-ray laboratories of the organic chemistry or physics departments to take diffraction photographs.

Several students recalled that Ramachandran was sometimes very angry and would scream at his students. Since their offices were all located in the cramped quarters of the lecture hall complex, all people in and around the building could hear about it. Consequently, when something like this happened, it spread across the campus rapidly. Just as day follows night, he would apologize the very next day to whomever was the target of his wrath the previous day. Everyone was fully aware of the tremendous breadth and depth of his knowledge in any field, so they tolerated these "aberrations." A standard joke of the time was that he would give a problem to one of his students and say "Take your own time and show me the results tomorrow." However, he was very enthusiastic when a student showed him some results, no matter how trivial. And he always had encouraging words for students and was never short on new ideas.

One of the most significant events for the institute in 1977 was Ramachandran's election to the Royal Society of London. For most Indian scientists, the Royal Society is a highly respected and prestigious organization, in which fellowship remained one of the most coveted vestiges of the British Raj. Many Indian scientists were elected as fellows during the British rule, but this number had decreased drastically after India became independent. Ramachandran clearly should have been elected to the Royal Society many years earlier, either in 1955 when he published the structure of collagen, or ten years later after he published the stereochemical criteria and the phi-psi diagram. But this recognition took nearly two decades. Dorothy Hodgkin, the famous Nobel Prize–winning crystallographer in Oxford who had determined the crystal structures of vitamin B_{12} and insulin, was instrumental in his nomination and subsequent election to the Royal Society. On their way to the United States, Ramachandran and his wife stopped over in London to receive the honor in a special ceremony at Burlington House, the seat of the Royal Society. Ramachandran performed the august duty of signing the register of fellows, which contains signatures of many illustrious luminaries including that of Sir Isaac Newton.

The period between 1972 and 1978 witnessed the rapid growth of the Molecular Biophysics Unit, but there was also tension and turmoil within the department. Ramachandran's mental health showed increased strain, problems that had begun to appear even when he was at Madras. He became extremely irritable and depressed. One of the unpopular things Ramachandran tried to do in those formative years was to start a post-M.Sc. diploma. He wanted to teach courses and wanted everyone in the department to teach too. Of course, no one liked it, and therefore no one was enthusiastic about it. As one faculty member put it: "I did not know how to handle him at that time, now I know what to do. He always wanted me to work on collagen. I would simply listen to him patiently, come out of his room, and do what I wanted to do. He would occasionally run his tantrums, and when it concerned me or affected me I was worried, otherwise I ignored it. I think his personality was too overpowering, and too overwhelming. But I think people in India did not quite appreciate his worth."

There were times when Ramachandran would be very happy, and there were times when he would be very angry. In fact, everyone in the department would bend over backwards to keep him happy. Sometimes he would say, "I see all of you going to the cafeteria for coffee, you are not inviting me to go with you." On the other hand if he was invited, he would say "Don't you see that I am busy?"

Part of the unhappiness in the department was also due to the fact that the faculty members were sharing crowded office and laboratory facilities. Since they did not have their own building and laboratories, they were scattered in different buildings and that made mutual interaction almost impossible.

There were vast differences in the hierarchical structure of the administration between University of Madras and the Indian Institute of Science. Madras had a pyramidal structure with one senior professor at the top who was in charge of the department and everyone else was of a lower rank or order. This was certainly true of the Physics Department in Madras, where most faculty members were former students of Ramachandran and they felt a special sense of indebtedness to their mentor. This was even reflected in the selection of their research problems.

The departments at the Institute in Bangalore had no such pyramidal structure. All faculty members had equal status, they were all separate and independent, and each had to prove his or her merits individually. The chairman of a department was simply an administrative head; the faculty members pursued their own independent research programs and applied for their own research grants. The system was, and is, similar to what exists at most American universities, where tenure and promotions are granted purely on the merits and achievements of each faculty member. Perhaps this was not easy for Ramachandran to get used to, and it caused some friction and unpleasantness between him and other faculty members.

It is interesting to note that there were two categories of faculty members in the Molecular Biophysics Unit: those who came with Ramachandran from Madras and those who were hired in Bangalore. The structure of the department in Bangalore allowed for free expression of opinions about how to administer academic programs for graduate students and how to conduct research programs. There were frequent discussions about how common resources were to be distributed. There also were arguments, even among the "originals," as to who deserved to get more favor from Ramachandran. No two individuals thought alike and it led to ill will among the faculty. Of course, it is not uncommon to have differences of opinion in departments with many diverse, young, bright, ambitious faculty, but there was a definite undercurrent of dissatisfaction in Ramachandran's department. As one faculty member described, "the atmosphere was very, very tense at every faculty meeting."

After Sasisekharan became chairman of the Molecular Biophysics Unit, his relations with Ramachandran were neither cordial nor pleasant. Some students would go to Ramachandran to discuss their research problems, and ask if such and such an experiment could or could not be done. Ramachandran would give his opinion, but apparently it was not proper procedure to engage in such discussions, especially if they were not his own students. Sasisekharan knew the rules of the institute and thought it should not have happened. Ramachandran did not know the rules, got frustrated, and believed that he was being deliberately excluded from such discussions.

As Chairman, Sasisekharan would write letters to the University Grants Commission, but they would send their reply to Ramachandran, not Sasisekharan—either because they were unaware of the administrative structure in Bangalore or because they considered Ramachandran the senior scientist. In any case, it was another source of unpleasantness within the department.

Indian science was also going through a period of turmoil. The gap between science done in India and that done in Europe or the United States was ever widening, with India lagging behind by several years. There was a general feeling among Indian scientists that their colleagues from the Western countries frequently ignored their work, and they didn't take time to read foreign journals. Instead they obtained their information about what was going on in their fields from telephone conversations with friends and by attending national meetings. When they actually visited India it was not necessarily to understand or interact with local scientists, but more for a holiday or vacation.

There were serious discussions among Indian scientists about what kinds of research problems were appropriate for "Indian conditions." Why was everyone rushing to publish papers in foreign journals? What was wrong in publishing in Indian journals? Curiously, even Indian government funding agencies were asking specific questions about the number of publications in foreign journals.

With qualified young scientists leaving the country and migrating mainly to the United States, the brain drain was a major problem in India. Jobs were scarce for such scientists in India and the level of frustration was very intense. When a department recruited a new faculty person, a junior candidate returning from outside India was sometimes preferred over a senior candidate from within India.

It was a great relief all around when Ramachandran received an opportunity to get away from Bangalore to spend some time in the United States. This happened in August of 1977, nearly six years after his last visit to the United States. He was invited to spend a year as a research scholar in the Fogarty International Center of the National Institutes of Health in Bethesda, Maryland.

18. Fogarty Center–Bethesda

The National Institutes of Health (NIH) in Bethesda, Maryland, is a conglomeration of research institutes dedicated to conducting research in the health sciences and finding ways to combat various diseases. The National Heart Institute, National Cancer Institute, National Eye Institute, and the National Dental Institute are among the research institutes at the NIH. One component of the NIH is the Fogarty International Center which organized a Scholars-in-Residence Program. Each year six to ten eminent scientists were invited to NIH for a period of six months to a year to conduct "studies of importance to biomedicine and international health" on problem of their choice. The invited scholars lived with their families in the "Stone House" on the premises of the NIH campus in Bethesda, where they ate dinner together and exchanged ideas in an informal atmosphere.

Ramachandran shared his tenure as a Fogarty scholar with several eminent scientists including Professors Howard Schachman of Berkeley, Nathan Sharon of Israel, and George Pickering, a physician from the University of Oxford. The Fogarty scholars held frequent discussions with other scientists at the NIH campus, visited universities and research laboratories around the United States, and gave seminars. All in all, it was a highly prestigious and intellectually satisfying assignment for the selected individuals.

As a Fogarty scholar, Ramachandran presented a paper on the influence of vitamin C on immune response at the Sanibel Symposium on Quantum Pharmacology, held in honor of Professor Linus Pauling. He was trying to understand one of Pauling's favorite hypotheses: Why is vitamin C good for health, in particular providing resistance to certain infections? The importance of hydroxyproline residues in stabilizing the collagen triple-helical structure was well known to Ramachandran. Proline hydroxylase is the enzyme that converts proline to hydroxyproline using Vitamin C as a cofactor. In a different but related field, Rodney Porter and his coworkers in Oxford were studying the complement protein C1q of the immune system and had shown that its linear sequence contained proline and hydroxyproline similar to that of collagen. The complement system participated in eliminating foreign molecules or pathogens attacking an organism. Ramachandran proposed that vitamin C might be essential for the synthesis and maintenance of hydroxyproline in the structure of the complement C1q, thus vindicating Linus Pauling's hypothesis.

Ramachandran also undertook a complete analysis of all possible secondary structures of polypeptide chains, including the alpha helix, beta structure, and collagen type triple-helical structure (designated as gamma helix). Gamma helix also occurs in polyproline II and polyglycine structures. Three such helices may occur side by side or be superhelically twisted around as in collagen; 3_{10} helix and beta turns are found in globular proteins. All these were right-handed helices. The only left-handed helix that was proposed for a polypeptide chain was the so-called omega helix, which occurred, for example, in poly-beta benzyl-L aspartate and related polypeptides.

In 1977, Oleg Jordetzky postulated the existence of another type of helical structure for a peptide chain that occurs as a part of the Lac repressor, which interacts with DNA through three Tyr residues on the protein. The standard alpha helix formed a hydrogen bond between carbonyl oxygen of residue n and the amino hydrogen of residue (n + 5), while in the new helix proposed by Jordetzky the hydrogen bonds were between the amino group of residue n and the carbonyl group of residue (n + 5). In Bangalore, Ramakrishnan made a thorough search of all possible types of single helices for L-amino acid residues and found that the only ones that can occur are of the types alpha (right- and left-handed), beta, 3_{10} (left- and right-handed), and gamma. He ruled out any other type of structure under the criteria adopted by him. At Ramachandran's suggestion, Chandrasekaran of Purdue University and Manju Bansal of the Indian Institute of Science also did energy calculations for various types of structures. All structures were reexamined, and it was concluded that the helix suggested by Jordetsky was theoretically impossible.

The dimensions of the peptide unit, its planarity, the bond angles, etc., can all vary by small amounts. In the lower left-hand quadrant of Ramachandran phi-psi diagram there existed regions of fairly good interatomic contacts and energy values. When the rigid conditions for the helices were slightly relaxed, new types of helical structures were possible with energies comparable to the stabilizing energies of the alpha helix and the 3_{10} helix. This was stable, however, only in the left-handed form and was forbidden otherwise. It had $n = -4.2$ (number of residues per turn) and $h = 1.23$Å (vertical rise per residue) and was superior in stability even to the left-handed alpha helix. The new structure was named "delta helix" and a detailed paper by R.

Chandrasekaran, T. S. Jardetzky, and O. Jardetzky was published (*FEBS Letters* (1979) *101*, 11–14). If Tyr occurred at every fifth position, the side chain phenyl rings will be nearly at right angles to the helical axis and assume an arrangement spaced by about 6.8A which would make it possible to intercalate readily with DNA.

While Ramachandran was in Bethesda, Sasisekharan and his colleagues in Bangalore were proposing an alternating helical structure of DNA. The main feature of this model indicated that it is possible to construct a left-handed helix for the DNA structure with practically the same values for the helical parameters as the accepted Watson-Crick right-handed helix. The Bangalore group also indicated that it is very likely that DNA in the cell may have a structure that is partly right-handed and partly left-handed, which would be alternating from one to the other at frequent intervals. This means that the net twist for a long stretch of DNA would be close to zero, instead of N/10 as would be the case for the Watson-Crick structure of N nucleotides.

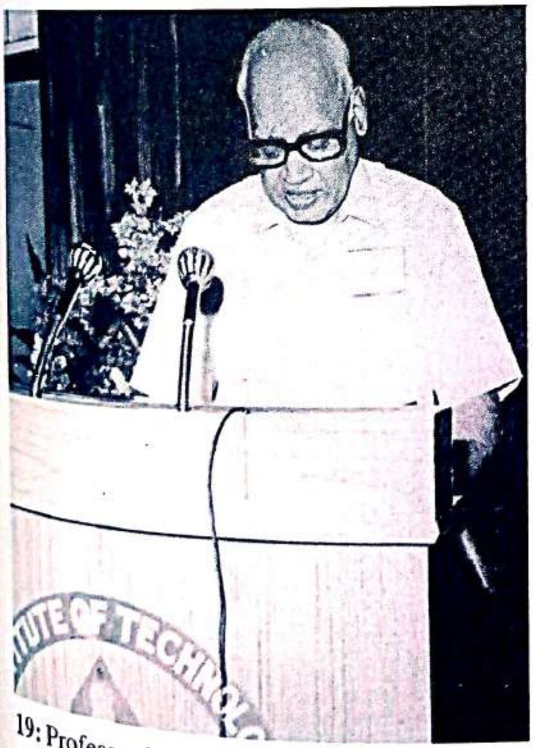
The alternating helical structure having no large twist in any one sense along its entire length is suitable for explaining the biological replication mechanism of DNA. The replication does not involve any large-scale twisting or untwisting. Similar results were obtained at about the same time by an independent group of scientists in Australia. Both groups published their results and a major debate ensued about the validity of the new DNA structure. Like many other scientists, Francis Crick, the original discoverer of the right-handed DNA double helix did not accept this new model for DNA.

Ramachandran presented the results of the alternating model in some detail at every laboratory he visited in the United States as a Fogarty scholar. Sasisekharan had provided him with a set of slides on the alternating DNA model, which became very useful for Ramachandran when he visited these laboratories. On such occasions, he obtained critical comments on the model, and suggestions to modify or improve the essential ideas developed in Bangalore, so that the model would be acceptable to biologists and X-ray crystallographers. In all, Ramachandran visited twenty-seven laboratories in England, Germany, and the United States as a Fogarty scholar.

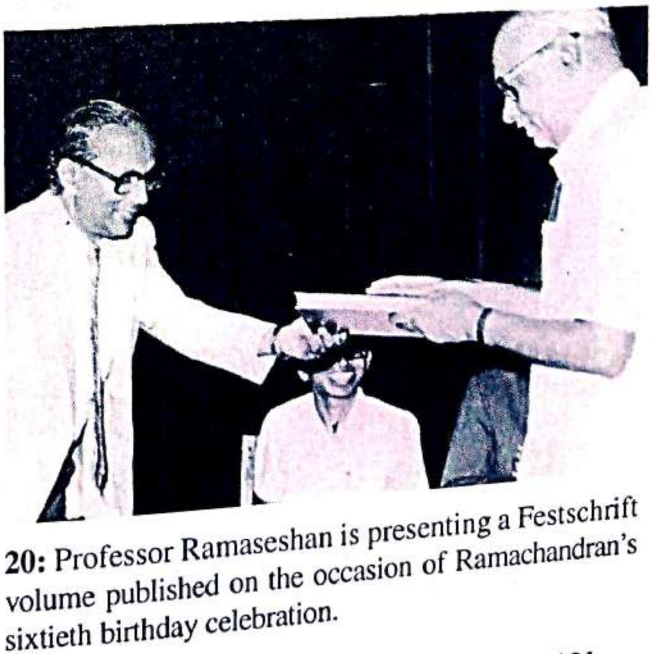
In summarizing his stay in the Fogarty Center, Ramachandran has said: "I will add only this one phrase about the rich fare of art and culture that was provided to us, namely that Washington is unparalleled. It was after a gap of some thirty years that I had the opportunity of being thrown into the company of persons with such wide outlooks and to be able to speak of "highbrow stuff", without being called a "snob". As a result, I have grown into a sort of "jack of all trades"—but I hope not a 'master of none'—and taken courage to give a popular talk on the 'Philosophy of Scientific Method' in the institute. I wish to thank the Fogarty Center once again for the unique opportunity provided to my wife and me to spend a year at the NIH."

17: Professor Ramachandran signing the book of Fellows of the Royal Society in the Burlington House in London. Drs. Vijayan and Blundell are looking on.

18: Professor S. Ramaseshan felicitating Professor Ramachandran during the latter's sixtieth birthday celebration held in The Indian Institute of Technology Auditorium in Madras in January 1982.

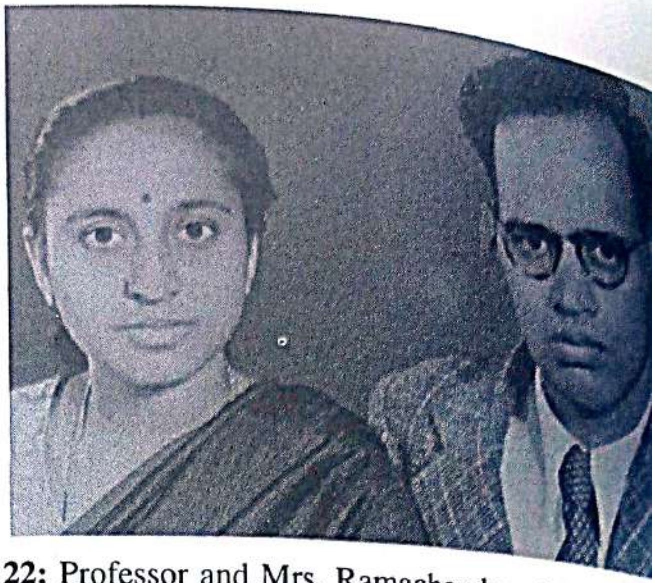


19: Professor Ramachandran speaking at his sixtieth birthday celebration in Madras.

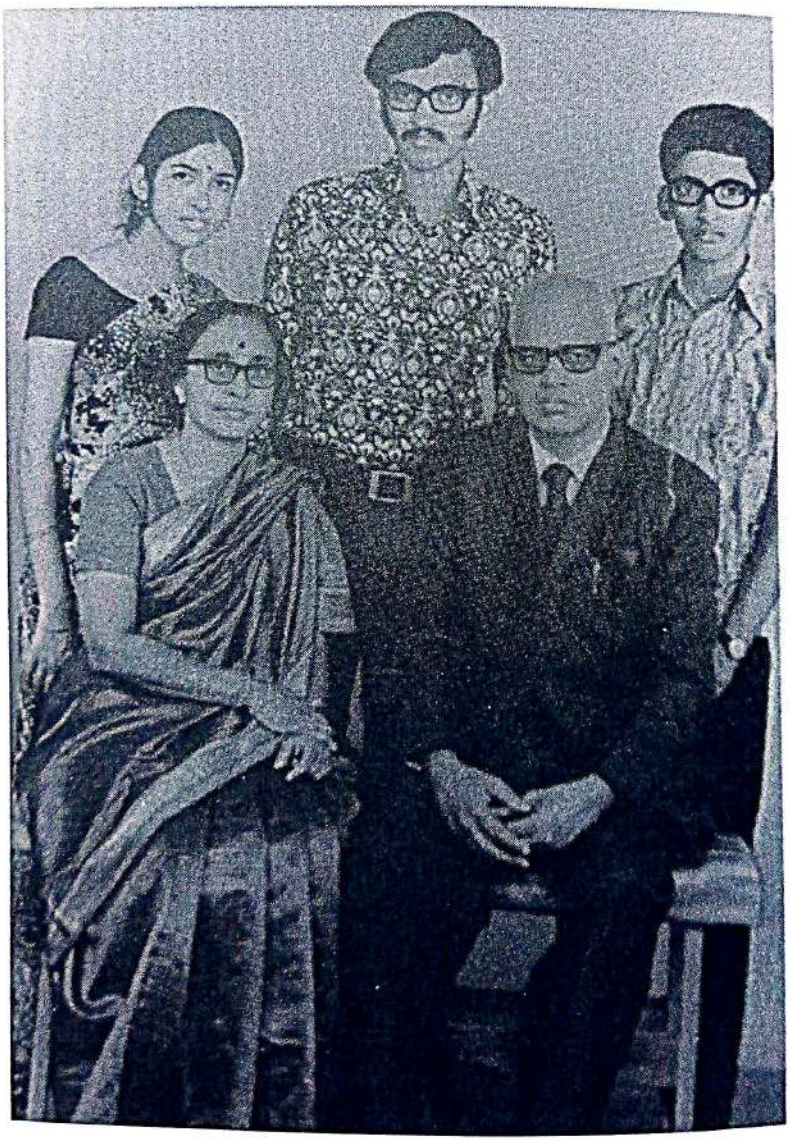


20: Professor Ramaseshan is presenting a Festschrift volume published on the occasion of Ramachandran's sixtieth birthday celebration.

21: Ramachandran's parents, Professor G. R. Narayana Iyer and Srimathy Ammalu Ammal.

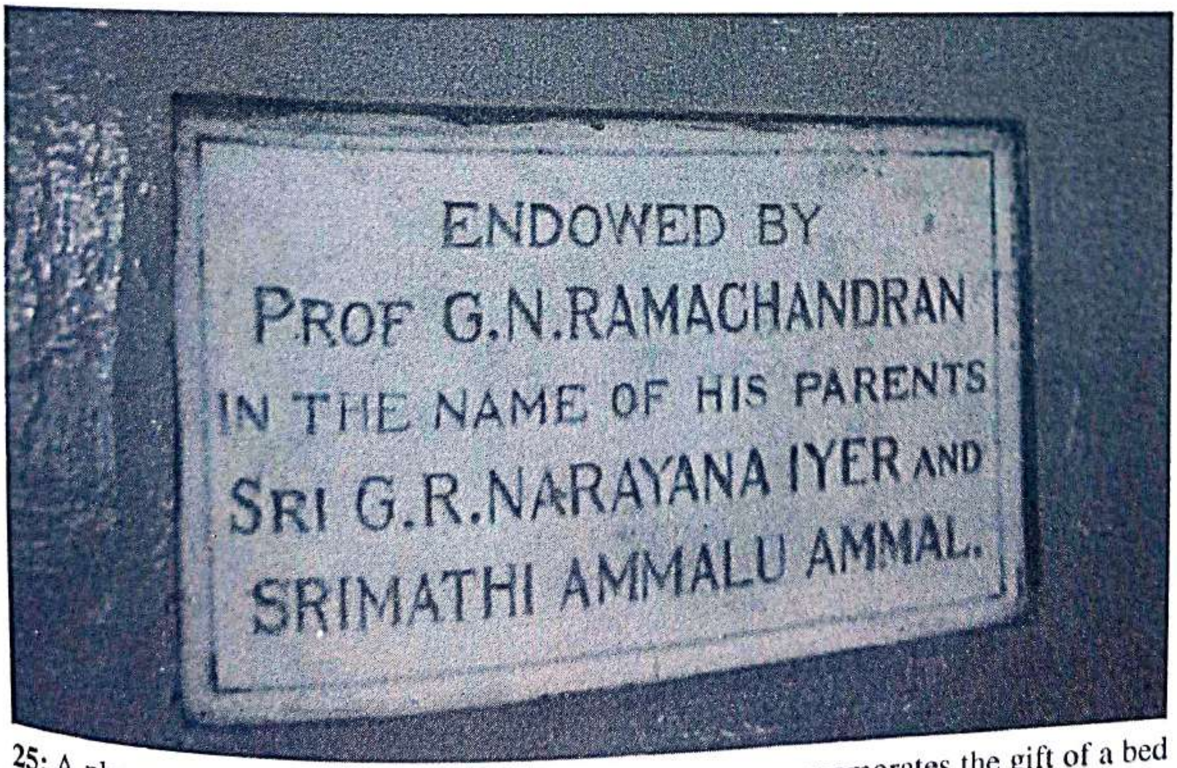


22: Professor and Mrs. Ramachandran (photo take in early 1950s).



23: An early photograph of Professor Ramachandran and his family (taken in the 1960s). Ramachandran and Rajam are seated. Standing are their daughter Vijaya, their first son, Ramesh Narayan and their second son Hari Narayan.

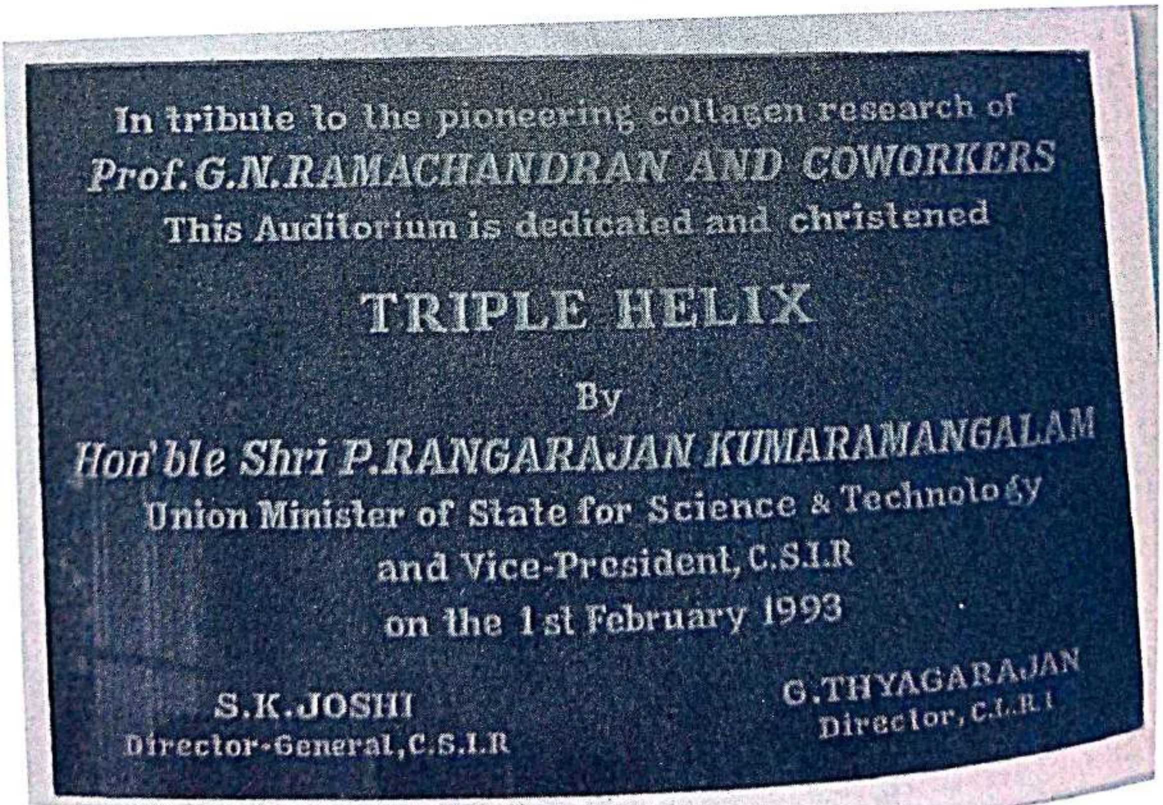
24: Professor and Mrs. Ramachandran (photo taken in 1997).



ENDOWED BY
PROF G.N.RAMACHANDRAN
IN THE NAME OF HIS PARENTS
SRI G.R.NARAYANA IYER AND
SRIMATHI AMMALU AMMAL.

25: A plaque in the Adyar Cancer Institute in Madras commemorates the gift of a bed endowed by Ramachandran in the name of his parents.

26: An impressive auditorium named "Triple Helix" in the Central Leather Research Institute in Madras. The building was named after the triple helical structure of collagen discovered by Ramachandran and Kartha in 1954.



In tribute to the pioneering collagen research of

Prof. G.N. RAMACHANDRAN AND COWORKERS

This Auditorium is dedicated and christened

TRIPLE HELIX

By

Hon'ble Shri P.RANGARAJAN KUMARAMANGALAM

Union Minister of State for Science & Technology

and Vice-President, C.S.I.R

on the 1st February 1993

S.K.JOSHI
Director-General, C.S.I.R

G.THYAGARAJAN
Director, C.L.R.I

27: A plaque commemorates the dedication of the auditorium in CLRI, Madras.

19. Mathematical Philosophy

In July 1978, Ramachandran returned to Bangalore. Sasisekharan was still the chairman of the Molecular Biophysics Unit, and lots of changes had taken place there. Several decisions, some of them controversial, were made at the faculty meetings in Ramachandran's absence.

One was the decision not to hire any new faculty members until the department moved into a new building, which was under construction. Several faculty members were away on sabbatical leave and they all signed a petition along with Sasisekharan recommending that there would be no new hiring in the department in their absence. Ramachandran was totally unaware of this development and was either planning to make some new recruitment or was in the process of negotiating with suitable candidates. All the junior faculty members met with Director Dhawan, explained their views on the postponement of new appointments, and obtained his support and endorsement. His colleagues' decision, even on a temporary basis, was a major disappointment for Ramachandran.

In the middle of this turmoil, everyone was apprehensive about how Ramachandran would react to the new changes, and there were things to frustrate him. He sensed that he was unable to motivate his colleagues in other departments to undertake joint projects of mutual interest. He attempted for two or three months to organize discussion groups between the biochemists and biophysicists to explore joint research possibilities. Unfortunately, there was no enthusiasm and no dialogue between members of the two departments.

He was eager to initiate new joint projects aimed at understanding the molecular basis of various diseases, for example the study of collagen in relation to arthritis. Again these initiatives went nowhere; there was no cooperation from his colleagues in the institute. Likewise, MBU protein crystallographers had considerable difficulty setting up collaborative projects with colleagues in the biochemistry department. Even obtaining small quantities of pure protein for doing crystal structure analysis was apparently difficult. Some alleged that the biochemistry department was more occupied in training students toward doctorate degrees, which would then also make it easier to crank out large numbers of publications.

When Ramachandran visited a number of laboratories in the United States as a Fogarty Scholar, he realized that crystallography had grown into a highly specialized computer-and equipment-oriented subject. He was convinced that it could not reach the same level of sophistication in India without a massive influx of funds, mainly in the form of foreign exchange. Making no headway in any new venture, his frustrations multiplied and he decided that it was time for him to change course.

There were rumors that Ramachandran was not happy with the situation and wanted to leave the MBU. The faculty members faced a serious predicament. If they agreed with him, he might feel that he was being driven out. If he remained, there would be continued tension. So when Ramachandran said he wanted to leave the unit, they neither agreed nor disagreed with him. Instead they politely suggested that he should do whatever pleased him the most. Eventually, the tension eased when Director Dhawan decided to appoint him as an Institute Professor in a new unit.

While in Bethesda, Ramachandran had become interested in the theoretical aspects of biology, which posed fresh challenges and new opportunities for him. He therefore accepted Dhawan's offer and considered naming the new unit "mathematical philosophy." Dhawan objected to the word "philosophy," preferring "mathematical biology" instead—maybe he didn't want a philosophy department in a science institute. It had to be either mathematical biology or theoretical biology.

Thus, in 1979, Ramachandran began a new endeavor in a separate office in the Institute's main library. (Though the name of his department would later change to mathematical philosophy when Dr. C. N. R. Rao became the new director). For all administrative purposes, this unit was associated with the physics department, chaired by Professor P. S. Narayanan, an experimental physicist, as well as a close personal friend and a great admirer of Ramachandran. Ramachandran severed all relations with the Molecular Biophysics Unit which he helped to create ten years earlier.

Ramachandran hired a computer programmer, and two secretaries, one to type personal correspondence and another for scientific manuscripts. He also hired a specialist in electronics to help him build circuits for testing and implementing some of the results he obtained on logical relations in information processing.

He wrote several interesting papers on an assortment of philosophical subjects, some of which were highly mathematical in nature. Consequently, he had difficulty publishing them in journals of mathematics or philosophy. Editors of the former group of journals suggested that his papers were appropriate for journals of philosophy and editors of the latter journals felt that the same papers were too mathematical for their readers. Ramachandran ended up publishing them in the institute itself as *MATPHIL* (for Mathematical Philosophy) *Reports*. They included over seventy papers on subjects ranging from Syaad Nyaaya, an aspect of Jain philosophy, to Kena Upanishad, one of the Upanishads in Indian philosophy and the relation between science, mathematics, and philosophy. Some of the reports dealt with the collagen structure, others with lattice dynamics, and one of them concerned the fundamental phase problem in crystallography. Some of them were based on invited talks he gave at different universities or associations in and around Bangalore. One of the masterpieces that Ramachandran wrote in 1981 was based on a plenary lecture presented by him at the second State University of New York at Albany Conversation in the Biomolecular Stereodynamics organized by Professor Ramaswamy Sarma, entitled "Biomolecular Conformation —Retrospects and Prospects (A Philosophical Review)." It was a remarkable personal reminiscence of some of his major achievements in the field of biomolecular conformations, and was a very engaging presentation filled with interesting anecdotes.

Ramachandran's stay at the Mathematical Philosophy Unit was by no means smooth and peaceful; it had its own ups and downs. He had no graduate students or postdoctoral fellows; he could not even arrange group meetings with faculty members in other departments of the Institute. There was just no interaction between him and other members in the Institute. Ramachandran felt that some of them were trying to avoid him. He dearly wanted a personal computer for doing numerical calculations, but there were no funds to buy one. Of course he had secretarial help, which was essential and useful because he was producing an enormous number of MATPHIL Reports.

One of the early MATPHIL Reports that he wrote in 1979 was on the subject of Syaad Nyaaya, also known as "the doctrine of may be." *Sayaad* means "maybe" and *Nyaaya* means "logic" in Sanskrit. According to Jainism, a very old form of non-Vedic religion born in India, any logical statement has more than two truth values, it may be true, it may be false, or it may be doubtful, meaning that it may or may not be true. Everyone easily understands the first two states but the third is not so obvious. An elaborate description of Syaad Nyaaya has been presented by Professor Hiriyanna, a philosophy professor of the Mysore

University, in his book *The Essentials of Indian Philosophy* (first published in 1949 by George Allen & Unwin Ltd., London, p. 59).

Ramachandran used mathematical operators, vectors, and matrices in Boolean algebra and expressed the above logical states into what he called "Boolean Vector Matrix Formulation" or BVMF for short. His entry into the realm of Syaad Nyaaya seemed like a natural and logical extension of the research he had done earlier. While he was working on the conformations of polypeptide chains, he began to question how unique the dihedral angles phi and psi were in describing polypeptide conformations. For a given stereochemically valid conformation, corresponding dihedral angles are fixed. Is the reverse true, i.e., for a given set of dihedral angles, is there a valid, possible conformation or is it doubtful?

In BVMF, vectors are used to represent the states of various input and output logical statements, and matrices are used to represent intermediate logical interconnections. A one-to-one correspondence is set up between matrix algebra and the interrelations among statements in an argument expressed by means of logical connectives. Thereafter it is believed that any problem, or theorem, in propositional calculus of logic can be solved and verified.

The logical operations OR and AND of standard classical logic are analogous to sum and product in Boolean algebra of genus 1 or BA-1. It has only 2^1 or two elements, represented as the binary digits 1 and 0. This can be extended by the use of BA-n, generated by n Boolean elements and 2^n states. BA-2 for example, represents all connectives of propositional calculus, via 2-element Boolean vectors, (T = (1,0), F = (0,1)) and 2 × 2 Boolean matrices. There are two new states in addition to TRUE and FALSE which are designated as follows: D for "doubtful" = $(T + F) = (1,1)$, and X for "impossible" = $(T \times F) = (0,0)$. This is the essence of the Syaad Nyaaya system (SNS). Ancient Jain philosophy had recognized the four states of SNS or BA-2 in their Syaad-Vaada or Syaad Nyaaya (Doctrine of Doubt). The truth state D described here "may be either true or false."

BA-3 with 3 independent generators has eight (or 2^3) states (7 possible and 1 impossible) and is analogous to what is called "quantified predicate logic." As described by Hiriyanna, the Jain philosophers had listed the seven possible states of BA-3 and called them "Sapthabhangi," the theory of seven parts. The various steps of the Sapthabhangi scheme and their corresponding Boolean vectors are:

1) for all, or may be a thing is; (1 0 0);
2) not for all, may be it is not; (0 1 1);
3) for some, may be it is and is not; (0 1 0);
4) all or none, may be it is inexpressible (1 0 1);
5) for none, may be a thing is not and is inexpressible (1 1 0);
6) there exists, may be a thing is and is inexpressible (0 0 1);
7) indefinite, may be a thing is, is not and is inexpressible (1 1 1); and finally
8) impossible (0 0 0).

Ramachandran worked out and published the BVMF of BA-2 and BA-3 in no less than 40 MATPHIL Reports during a period of eleven years from 1979 to 1990. He described matrix algebra and computer programs for predicate logic and extended predicate logic. He even designed a "Syaad Nyaaya Yantra," Syaad Nyaaya machine to work out solutions for various logical statements.

One of the simple applications of BVMF is to help understand a number of paradoxes that exist in the literature. Paradoxes and antinomies are commonly present in the literature of logic. Such a paradox has no solution in classical logic. However, it can be shown to have two solutions in SNS—doubtful (1,1) or contradictory (0,0). It can also be shown to have an interesting solution in the Sapthbhangi logic—(0,1,0)—corresponding to the result that "a statement exists but is not provable to be definitely true or definitely false." Some examples follow.

Consider the statement "What I say is false." Is this statement true or false? The usual answer is that if the statement is assumed to be true (T), then the consequence is that the statement is false (F). On the other hand, if the statement is taken to be false (F), then the consequence is that the statement is true (T). We thus have a paradox. If this statement is fed into matrix calculus in the form stated above, and a computer is given the problem of checking whether it is true or false, then it will go on printing a series of continuous outputs—T, F, T, F, . . . etc. "What I say is false" the well-known paradox of the liar. The usual way of blocking such paradoxes in standard logic is to avoid formulating the truth conditions for statements of a language or logic, written in that language itself.

Suppose the statement is restated as: "If what I say is true, then it is false," i.e., in the form of an implication, (A is true) ===> (A is false). Then if T is fed in for the input state, the output will be F; if F is fed in, the output is only D; and, on repetition, the process stops there, because D can thereafter give only D. In other words, the conclusion is that the statement A can give no definite information and has the indefinite D state.

A second paradox says: "The barber of Seville shaves all those who do not shave themselves. Does he shave himself or not?" One of the two following possibilities is valid. It is an impossible or contradictory statement in logic, so that it may be concluded that the barber of Seville does not exist, or it is perpetually doubtful whether the barber of Seville shaves himself or not and no definite information on this can ever be obtained from this line of inquiry.

In one MATPHIL Report, Ramachandran elaborates on another interesting paradox from the ancient Hindu philosophy used to describe the Divine Force of the Universe in Kena Upanishad: "If you think you know It, then you do not know It, and if you know that you cannot know It, then you know It." This statement conveys perpetual doubt and indefiniteness.

The new BVMF method described by Ramachandran still provides a practical technique of testing the validity of arguments, including proofs of mathematical theorems.

Ramachandran's faith in mathematics is intense as this quote from one of his MATPHIL reports illuminates: "I think that there is no doubt that natural science can be made fully mathematical ultimately. A good physicist must be a theoretical physicist; a good chemist must be a physicist and must know mathematical theory. A good biologist must be a good chemist and must be therefore a good physicist. Therefore, one cannot be sufficiently good in biology unless he has a mathematical instinct, although he may not be proficient in actually applying mathematical methods to his specific problems."

20. Hyderabad & Back

Even the mathematical philosophy group at the Institute did not work out as well for Ramachandran as he might have hoped. During the period between 1978 and 1982, he hired a computer programmer and a technical assistant to write computer programs and also to help build some electronic circuits to apply the results of Syaad Nyaaya for information processing. Ramaseshan, who succeeded Dhawan as institute director, did not see eye to eye with Ramachandran on many matters. The close relationship between these two eminent scientists who had known each other for nearly four decades was unfortunately deteriorating.

In 1981, Ramachandran felt that it was impossible for him to continue not only in the institute but also in Bangalore, and so he decided to leave. He moved to the Center for Cellular and Molecular Biology (CCMB) in Hyderabad, a pioneer institution developed by Dr. Pushpa Bhargava, a well-known molecular biologist. Getting Ramachandran to Hyderabad was a great accomplishment for Dr. Bhargava, even if it turned out to be for too short a time. Though the move was actually initiated by Ramachandran, for once Dr. G. S. Sidhu, the director general of the Council for Scientific and Industrial Research, moved extraordinarily fast. Ramachandran was offered the post of Distinguished Scientist at the CCMB, an honor bestowed on senior retired scientists who continued to be scientifically active and productive. The appointment provided a research grant which included a monthly salary and complete intellectual freedom to do any kind of research or establish any type of experimental facility in crystallography or in biophysics.

Unfortunately, even this new venture did not last too long. Ramachandran's move to CCMB in Hyderabad was perhaps too premature. At the time, an ultramodern research facility was still mostly in the planning stages and construction had barely started. All the scientists were located in different buildings, the library facilities were inadequate, and mutual consultation and collaboration was not possible. Ramachandran also found out quickly that the intellectual atmosphere in Hyderabad was not as rich and varied as in Bangalore. The weather in Hyderabad tended to be unbearably hot most of the year, contrary to Bangalore which is well known for its moderate climate. In addition, the infrastructure in Hyderabad needed a lot of improvement. A simple thing such as a telephone was not available for

Ramachandran's use and he was told that it would take two years before he could get one in his residence. Even the simple task of arranging for a doctor's appointment created enormous logistical problems. It is not surprising that Ramachandran returned to Bangalore in less than four months. Fortunately, the Ramachandrans still owned their house in Malleswaram in Bangalore and so resettling was not too difficult.

Now the Center for Cellular and Molecular Biology in Hyderabad is one of the foremost research institutions in India, very well equipped for doing state-of-the-art research in molecular biology. It has successfully attracted and employed several eminent Indian scientists returning from abroad who are now doing outstanding research in their field. Ramachandran would find today's atmosphere extremely pleasant, even though the weather in Hyderabad is still as hot as it was when he first went there.

In 1982, Ramachandran turned 60 years old. In India the normal mandatory retirement age for every one but politicians is 58 years and extensions are granted only under extraordinary circumstances. Ramachandran, nevertheless, continued his assignment as a Distinguished Scientist of the CSIR, which graciously allowed him to work from his own home. He had already resigned from the Indian Institute of Science and so there was no question of his going back there and he simply did not want to return under the administration that had him go to Hyderabad.

Between 1982 and 1984 Ramachandran did most of his research at home in Malleswaram. However, by the end of 1982, Ramachandran wrote to the CSIR that he did not want to take any salary as a Distinguished Scientist. So from January 1983 to August 1984, though he earned no salary, he continued to do research at home. The secretary who had worked for him at the institute would come every morning to take routine dictation of letters and manuscripts. For administrative purposes, Ramachandran transferred his CSIR fellowship to the National Aeronautical Laboratory in Bangalore. Obviously he did not want anything to do with the institute. Was there a similarity between what was happening in case of Ramachandran and what happened to his mentor, Sir C. V. Raman, four decades earlier?

It is traditional in most academic institutions to felicitate a celebrated scientist's 60th birthday with a party and a symposium or at least a public meeting. Ramachandran was a distinguished scientist, a famous alumnus of the institute, and a founding member and chairman of a department in the institute. Yet surprisingly no one in the institute was forthcoming with plans to celebrate his birthday. True, he was no longer a full staff member, but he had contributed much of his life to the progress of science at the institute. No matter how one looked at it, it was an unfriendly gesture on the part of his colleagues at the institute and seems unjustifiable; it simply defies rational explanation.

But the Madras group had not forgotten Ramachandran. In spite of the fact that he had long since left Madras University, Professor Srinivasan and his colleagues organized an elaborate birthday ceremony. They arranged an international symposium in his honor. A number of distinguished scientists, from all over the world, including many past students, attended the symposium and delivered lectures on various emerging aspects of conformational biology and its principal tool, X-ray diffraction. There was an outpouring of respect and admiration for the scientific contributions of Professor Ramachandran. Ironically Ramasheshan, who was then director of the Indian Institute of Science, presided over the ceremony and presented an elegantly prepared Festschrift on that occasion; it was a most delightful and moving ceremony.

Speaker after speaker congratulated Ramachandran, wished him well, remembered their association with him, and recalled his contributions to the advancement of biophysics. When finally it was his turn to speak, he was overcome by the emotions of the moment and he said only four words with tears of appreciation. "Thank you, thank you" he said simply and returned to his chair.

In 1984, the Indian National Science Academy (INSA) celebrated its golden jubilee and created five special research professorships. The first one, the Albert Einstein Professorship, was offered to Ramachandran. It was a great and coveted honor, properly bestowed on an outstanding senior scientist in India. This four-year appointment gave the recipient full freedom to work on any subject of his choice. By now, Professor C. N. R. Rao was the new director of the institute. He visited Ramachandran and requested that he return to the institute. He designated Professor P. S. Narayanan, chairman of the physics department, to be in charge of all his needs. Ramachandran was given generous office space for his research and resumed work in the Mathematical Philosophy Unit.

In a brutally frank interview, Professor Rao described how disgraceful it was that Ramachandran was not honored with a Padma Vibhushan; a title bestowed by the Indian government on distinguished

Indian citizens. Rao himself had received the title and so had many other contemporary and perhaps less deserving scientists. He said that he nominated Ramachandran several times, even when he was not on the selection committee. Later the government decided to do away with all such honors. Professor Rao also felt that Ramachandran should have received the fellowship of the Royal Society, much earlier.

According to Professor Rao,

> Ramachandran was not given proper recognition at the right time. If we had done that, maybe he would not have suffered so many nervous breakdowns in his life. I think he picked the wrong protein; collagen is not a glamorous molecule. He was working in a rough area. Even under the most favorable circumstances, it would be very difficult to get a Nobel Prize, but he is certainly the Nobel Prize caliber; he is in the same class. His was a good example of a case where recognition and a pat on the back would have done a lot of good.
>
> I think some people in the Molecular Biophysics Unit were afraid that Ramachandran would steal their ideas and talk about it everywhere. In fact, he would talk sometimes about my own work. I did not mind that at all.
>
> When Ramachandran was 60 years old, I wanted the Academy [Indian Academy of Sciences] to produce a Festschrift in his honor. I was the president of the Academy at that time, but they did not do it. Later, in August of 1991, they collected together a number of invited articles and published a special issue for him. But there is a time for everything and they should have produced a Festschrift at the proper time. They have done it for several other people, some probably did not even deserve it. I know that even those scientists who think very highly of him failed to give him his due at the proper time. It is a kind of benign indifference, or what shall I say, not giving him his due.
>
> We should have never allowed him to leave the MBU. There was some bad episode in the MBU and he left. Granted that he had his own faults, but they should have tolerated it. After all, he was getting to be an old man. Molecular biophysics was his strong point and that was what he was good at. We should have done everything to allow

> him to continue to do that. It is very sad. Even now the younger people should forget all that happened in the past and go and talk to him. It was he who started that department. I know he has not returned to MBU after he left it.
>
> I know when I got my Fellowship in Royal Society, you see the fellows get the list as soon as it gets published, so he was in Hyderabad and he called me and congratulated me. I remember, it was exactly five years after he became a fellow of the Royal Society. I do not know what happened in Hyderabad. I certainly wanted to support and do everything I could for Ramachandran. I was very happy that the CSIR gave him their Golden Jubilee Award. I was also happy that GNR got the Nehru award. I am very happy that I could do something to show my respect and my support of this great man.

In 1989, Ramachandran gave up his Einstein Professorship when he went to the United States to visit his children. Since his return in 1990, he has continued his research without any grants from his home. This scientist never ceases to work.

In 1990, amidst all his work on mathematical philosophy, Ramachandran published an interesting paper on the phase problem in crystallography. Surprisingly, it drew very little attention even among crystallographers. On the other hand, an almost identical paper published a year later by an investigator in the United States received considerable attention and application. Both papers appeared in the same journal. It was even more outrageous when the author of the second paper, another Indian, failed to cite Ramachandran's paper. This represents the very sad code of behavior in scientific research one encounters periodically. (Ramachandran, *Acta Cryst, A46*, 359–365(1990); S. Subbiah, *Science* 252, 128–131 (1991); S. Subbiah, *Acta Cryst, D49*, 108–119 (1993).)

In his paper Ramachandran described a new direct method for determining the phase angles of reflections in the diffraction pattern of a crystal. The amplitudes and the phase angles are required to calculate the electron densities of molecules in a single crystal. Ramachandran, a master in the art of nomenclature, called the new method *RAGA* for "Real-Atom Grid Approximation" of crystal structure analysis in the initial and intermediate stages*.

*RAGA also refers to a distribution of the scale of notes in Indian classical music. Different compositions in classical music are set to different ragas and there are hundreds of ragas in the classical music system.

The electron density distribution in a crystal is approximated by a set of atoms distributed randomly over a grid forming a sublattice of the unit cell. The observed structure factor is compared with the calculated structure factor for the grid atom structure and a standard least-squares refinement procedure is used to move the atoms of the approximate structure to their final correct positions. It may be necessary to perform a very large number of least-squares refinement cycles before the final solution is reached. Usually one starts with a low-resolution data and gradually adds more data and increases the resolution.

Ramachandran not only worked out the theory, but also applied the method to structures of small molecules especially in two-dimensional projections. He wanted to extend it to the case of biological macromolecules, but had neither the manpower to do the calculations nor access to a super-computing facility in the institute. The investigator in the United States used exactly the same or similar principles and actually applied the method for solving one or more structures of biological macromolecules. There was only one paper that Ramachandran wrote on this subject. The method is still being developed and used in solving protein structures.

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21. Psychiatric Problems

As mentioned previously, Ramachandran is a very temperamental person. This was one of the qualities largely misunderstood by many of his friends and colleagues alike. In fact, many people associate him with two characteristics—his extraordinary intellectual ability and his unusually temperamental nature. It is not clear when this behavior actually sprouted or what triggered it. Neither Ramachandran nor his family wants to conceal the problem in any manner or prevent discussion about it. It is no secret that Ramachandran received and continues to receive psychiatric help.

Ramachandran suffered a series of disappointments right from the beginning of his scientific career. That alone may have had something to do with his mental illness. Kartha and Ramachandran were the first to propose a coiled-coil structure for collagen. The importance of this discovery was overshadowed by Rich and Crick's criticism of this structure, as well as Watson and Crick's discovery of the double helical structure of DNA. Collagen was simply not DNA and did not have the same glamour.

There were no computers in Madras in early 1950s to enable the investigators to perform a refinement of their model when the structure of collagen was proposed. Kartha and Ramachandran had to use local homemade tools for model building and measuring bond distance and angles. Rich and Crick vehemently criticized the collagen structure for alleged short contacts, and there might even have been a deliberate attempt to delay publication of Ramachandran's paper. For a young scientist barely in his thirties all of this must have been a devastating blow, certainly serious enough to cause a nervous breakdown.

Fortunately, it did not have any lasting detrimental effects on his productivity or creative ability in the field of molecular biophysics. Obviously though, it had a serious side effect on his relations with other people, his family, scientists and non-scientists, students, colleagues, and friends. He was apt to lose his temper swiftly, though he would be equally quick to apologize to the injured, be it his secretary, student, or colleague. He was always frustrated at not being able to do all he wanted to do, be it a joint research project with other scientists or even an administrative matter like a post-M.Sc. diploma. He would often conclude that those around him were not cooperating, he even believed that there was some conspiracy against him. Psychiatrists call this "paranoid schizophrenia."

For example, he believed that others were doing experiments harmful to his brain, influencing his thinking, interfering with his creativity, and preventing him from being a great scientist. He believed that radio waves were being used in such experiments. He asserted that he was not under any delusion, but that it was all real. As a scientist he believed that such experiments with electromagnetic waves were indeed feasible and this created a lot of anguish for himself, his family, his doctors, and all his friends.

Because of this delusional thinking he often thought he was not performing at the peak level of his capacity. Fortunately, his scientific thinking, logic, or reasoning power was not disrupted. Those under such delusions are often treated in mental hospitals, but this was not necessary in Ramachandran's case. In most respects, he led a normal life. He was very much interested in classical music; he could talk on a wide range of topics, including philosophy, politics, or anything else, in a most cogent and persuasive fashion. In other words, his mental illness did not invade other spheres of his activities.

Ramachandran and his wife met a British physician, Dr. George Pickering, when they were at the Fogarty Center in Bethesda, Maryland. Dr. Pickering, who was a Fogarty scholar during the same period, had proposed the hypothesis that many scholarly people would not have been as creative and productive had it not been for their psychological problems. Without such problems they would have been just "ordinary" people. In his book entitled *Creative Malady* Dr. Pickering analyzes the lives and minds of luminaries like Charles Darwin, Florence Nightingale, Mary Baker Eddy, Sigmund Freud, Marcel Proust, and Elizabeth Barett Browning to explain his hypothesis.

Dr. Pickering argues that illness, particularly psychological illness, may be an aid to creative work and indeed essential in some cases. Illness that is not debilitating, disabling, or life-threatening may be ideal for creativity. Charles Darwin suffered from an obscure illness for most of his life; it was a kind of psychoneurosis, which protected him from the trivialities of social intercourse. Illness provided him the solitude and leisure needed to develop and support his revolutionary concept of evolution, as he himself recognized. The nature of Darwin's illness has been a subject of great discussion and controversy. Dr. Pickering cites four more examples that satisfy his definition of creative illness, Joan of Arc, Mary Baker Eddy, Sigmund Freud, and

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Marcel Proust.

There is no a priori reason why psychoneurosis should not indirectly benefit society at large as well as benefiting its victim. Dr. Pickering's examination of Darwin and others, their achievements and their illnesses, has led him to conclude that the world is indebted to their illnesses for the great contributions they have made in their own times and to posterity. Without that illness the great work would not have been done, or done in such splendid style. That is what he means by creative illness. Dr. Pickering hoped that an understanding of the occasional usefulness of psychological illness would induce a more tolerant attitude by society.

What is mental illness? The dividing line between mental health and mental illness is by no means clear-cut, nor is the division between the classes into which mental illness is commonly divided. Mental disorder is divided into the more severe psychosis, and the less severe psychoneurosis.

Manic-depressive psychosis is a condition in which a mood of extreme exaltation and intense energy is followed by a mood of deep depression and inactivity; interspersed with varying periods of normal behavior. In the manic stage, ideas follow from one another with extraordinary rapidity. These ideas, combined with the intense energy, may lead to achievements and creations of the first rank. Depression is characterized by deep gloom; the subject feels that he is guilty of all kinds of errors of commission and omission; that he is utterly incompetent, and incapable of performing any useful service.

Schizophrenia may be the most common psychosis. It begins with a failure of social adjustment, which may seem an exaggeration of manifest difficulties, produces a complete disintegration of personality. Many of those who achieve distinction are hypomaniacs in whom mood swings from one of energy, exuberance, and confidence, to one of the reverse. Freud was an example. Such people are quite sane, and as long as circumstances do not press too hard, are in no danger and often achieve great things.

Many creative people have a schizoid character; i.e., they play a mixture of the opposites. According to Dr. Pickering,

> . . . there are five ways in which a schizoid character aids creativity. First, most creative activity is solitary. Second, creative activity enables a schizoid person to retain at least

> part of his fantasy of omnipotence. Third, creative activity, for the schizoid person, reflects his own scheme of values in which the characteristic feature is that a greater importance is attributed to inner reality than to external world. Fourth, certain kinds of creativity are peculiarly apt for overcoming the sense of arbitrary unpredictability. Fifth, creative activity can undoubtedly act as a defense against the threat that overhangs the schizoid person of finding the world meaningless. The schizoid personality of Einstein and Newton fits this description.

Does Ramachandran's mental illness fit this description? Did his illness foster his creativity? There are lots of similarities to some of the personalities described above. Sigmund Freud, for instance, very strongly believed that he was a great scientist and deserved the award of a Nobel Prize for his discoveries. He was deeply disappointed when he did not receive one. Similarly, disappointment and frustration constantly tormented Ramachandran throughout his scientific career. Did it lead to his mental illness, and did it in turn facilitate more creative endeavors?

Ramachandran never felt that he was actually competing; he only wanted to know the correct answers to the problems he was working on. Obviously, this was not true in his early career when he started his research on structure of collagen. He was indeed competing and wanted to be the first to come up with a correct structure. He did come up with the novel idea of a coiled-coil structure for collagen. Then spent more than a decade defending the two bonded-structure. He was quite frustrated by that effort, even by the very idea that he had to defend his proposed structure. Other investigators in the field had used his ideas and developed similar structures without properly acknowledging his contribution. He strongly believed that the difficulties he experienced and the reason why his contribution was not properly recognized was simply because the work was done by an Indian—"How can an Indian do something that we could not do?"

The psychological torment and the associated massive doses of medication may have indeed caused more problems for Ramachandran, namely the Parkinson's disease that currently afflicts him. He has also suffered some minor speech difficulty in the later years of his life.

Parkinson's disease makes his muscles very rigid, he does not have the flexibility to use his muscles as we do, once he starts walking; it is very difficult for him to stop, or do anything else suddenly. Parkinson's disease is not completely curable. Before a long conversation, he prepares himself with a suitable dose of dopa, the standard medication for the Parkinson's disease.

In Ramachandran's case, the paranoid schizophrenia resulted in the notion that others were interfering with his thought process. Psychiatrists call it a symptom, but he calls it "his experience" and it seems perfectly logical to him. He tries to explain it with high-sounding technical terms that most people do not easily understand. From what we now know, mind reading and reading other people's thoughts do not seem possible; they are illogical. He, however, is convinced that other people are indeed trying to read his mind and experiment with his brain using radio waves.

Several people have described how Ramachandran would abruptly stop talking during one of his public lectures or seminars. There would follow an embarrassing silence as the host ran around trying to get a glass of water. After a couple of minutes, Ramachandran would regain his composure and continue his lecture as if nothing had happened.

Most individuals suffering from this malady are also egotistic, to a certain extent, and have an exaggerated feeling of self-importance. Ramachandran personally knew and had heard other people talk about his extraordinary intelligence and tremendous depth of knowledge. He was often surrounded by students and people who sometimes blindly admired him. Individuals such as Ramachandran suffer a monumental fall and are terribly hurt if anyone dares to oppose them or suggest that their ideas may be incorrect.

22. Ramachandran, The Human Being

There is a totally different side to Ramachandran's life that is not apparent to those, who know him only as a scientist. He is a dedicated family man, a devoted father, and a very great philanthropist in every sense of the word. He has two sons, one daughter and a grandson. All of his children have doctorates in different subjects, upholding the family tradition of outstanding intellectual achievement. Ramachandran and his wife Rajam are justifiably very proud parents.

Their first son, Ramesh Narayan, obtained his doctorate in crystal physics from the Raman Research Institute in Bangalore and later changed his research interests to astrophysics. He is currently a professor at the Harvard-Smithsonian Center for Astrophysics. Their daughter, Vijaya, got her doctorate degree in computer science from Princeton University in the United States, and is currently a professor in the Department of Computer Science at the University of Texas in Austin. Their youngest son, Hari Shankar, obtained his doctorate in plasma physics from University of California at Berkeley and is a senior scientist at the Institute of Plasma Research in Ahmedabad in the State of Gujarat in India. Hari Shankar is the father of a son born in 1995, the same year Ramachandran and Rajam celebrated their fiftieth wedding anniversary. What a splendid gift to receive on such a happy occasion.

Ramesh Narayan remembers how his father influenced his early interest in mathematics just as his grandfather had motivated Ramachandran himself. Ramachandran would challenge young Ramesh with puzzles, mathematical problems, and logical paradoxes. Sitting in the terrace of their residence in Madras after dinner, Ramachandran introduced his son to constellations, planets, and stars and other simple astronomical observations. This early introduction had a profound effect on Ramesh who has chosen modern astrophysics for his career.

Ramesh was advised by his father to study physics in college. Apparently Ramachandran, as a physicist, felt that persons who learn physics can then move on to whatever field they liked. Ramachandran gave the same advice to Vijaya and Hari. Vijaya indeed studied physics as an undergraduate but subsequently switched to electrical engineering and computer science. Hari on the other hand studied electrical engineering as an undergraduate and changed over to physics for his postgraduate and postdoctoral studies.

As noted earlier, Ramachandran married Rajam in 1945 before his Cambridge trip for a second doctoral degree. Rajam has been an extremely influential person in Ramachandran's life. It was probably not easy being the wife of a famous scientist, whose sole preoccupation was science. Science was an obsession with Ramachandran; he could not divert his attention until a satisfactory solution had been found to every problem he was investigating. Even at the dinner table, he could be totally oblivious to the conversation around him, and would remain silent for a long time. His mind would be somewhere else; then, all of a sudden, he would talk about something scientific that they were discussing a long time ago. This must have created trouble, at least in the early years when the children were still growing. Then followed his psychiatric problems in Madras. Surprisingly, the children knew very little of their father's problems, their mother successfully isolated and insulated them from what was going on with their father.

Once, soon after their marriage, Ramachandran visited Rajam at her parents' house in Nagpur in Central India. Ramachandran either forgot or simply did not know that he should take some gift for his beloved wife. Having realized it late, he presented her with a collection of reprints of his published papers!

Ramachandran and Rajam are extraordinarily magnanimous. Their donations and contributions to charitable institutions are exemplary, but their modesty prevents them from talking readily about this subject. For example, in early 1960 Ramachandran made a generous donation of 5,000 rupees to the Adyar Cancer Institute in Madras for the purpose of establishing a bed in the name of his mother. One day on his way home from work, he simply walked into the Cancer Institute, asked for the director, and wrote a check for the donation. This happened just as he was starting his career as a professor at the University of Madras. His father, who was alive at the time, reminded his son that he had a young family to care for and had to save for their education. A plaque commemorates this donation over a bed in the Adyar Cancer Hospital.

Ramachandran has received over a dozen awards at various times. In almost every case, he has donated the monetary component to some charitable organization or instituted awards of his own in various educational organizations in Madras and Bangalore.

1. Shanti Swarup Bhatnagar Prize for Physical Science (1961)

2. Watumul Memorial Prize in Biophysics (1964)
3. John Arthur Wilson Award by American Leather Chemist Association (1967)
4. Meghnath Saha Medal of the Asiatic Society (1971)
5. Srinivasa Ramanujan Medal of Indian National Science Academy (1972)
6. J. C. Bose Award of University Grants Commission (1976)
7. J. C. Bose Award of the Bose Institute (1977)
8. Fogarty International Medal of the NIH (1978)
9. Indian Institute of Science Alumni Award (1979)
10. Sir C. V. Raman Medal of INSA (1982)
11. R. D. Birla Award for Medical Sciences (1985)
12. CSIR Golden Jubilee Award for Life Sciences (1991)
13. M. P. CSIR Jawaharlal Nehru Award for Science (1992)

In 1985, he donated the cash prize that accompanied the Birla Award for Medical Sciences, the very large sum of 100,000 rupees, to the Prime Minister's National Relief Fund to help the victims of the chemical disaster at the Union Carbide factory in Bhopal in Madhya Pradesh. They discovered that there was no special organization dedicated for this purpose and all donations were being received by the National Relief Fund.

It is ironic to note what happened to one of the awards that Ramachandran received outside India. The American Leather Chemists Association selected him to receive the John Arthur Wilson Award in 1967 for his contribution in the field of collagen, the results of which directly related to leather chemistry. The award included a large plaque, which was presented to him in the United States. Since he did not want to carry it with his personal luggage to India, he asked them to ship it to his home address. When the package arrived at the Madras port, it had to be cleared by the customs officials. The officer on duty determined that Ramachandran had to pay 2,000 rupees toward import duty. His explanation that it was an award and not something that he had purchased failed to convince the officer. Reluctantly, Ramachandran left the package with the customs officer. None of the administrators were able or willing to relax the rules and make an exception; the package disappeared, never to be seen again. A classic example of bureaucratic indifference and insensitivity, this is how much the country appreciates the recognition accorded to one of its well-known scientists. The award is probably decorating the mantel-

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piece of some customs official.

One of the most suitable tributes paid to Ramachandran happened in 1993 when the Central Leather Research Institute in Adyar, Madras, constructed and dedicated a large auditorium on their campus to the "pioneering work on collagen by Ramachandran and his coworkers." Most appropriately they named the auditorium "Triple Helix" to commemorate the famous model for the collagen structure proposed by Ramachandran more than four decades earlier. The magnificent structure stands proudly in the Madras sunshine for all to see and remember Ramachandran's contribution to molecular biophysics.

Ramachandran trained numerous graduate students who obtained their doctorate degrees under his able guidance. A complete list is presented in the Appendix. In this achievement only his own mentor, Sir C. V. Raman, matches him. Many of these students have gone on to become leading scientists in the field of biophysics in different parts of the world and all of them owe their success to the training they received in Ramachandran's laboratory.

Ramachandran learned from C. V. Raman that "we have to find our own way rather than follow the literature." This was not always very efficient because he spent too much time reinventing the wheel. Being a very intuitive person he often succeeded in deriving various results himself and became convinced that he had discovered something new. He had no patience to read the current scientific literature, especially during the later years in his career and often found out about advances in his field by talking to other scientists. But he was intellectually honest and did not take any credit when it was not due him. As a student he spent several years with Raman, but surprisingly they did not publish a single paper together. Raman must have concluded that the work presented in those papers was solely Ramachandran's and did not deserve joint authorship. Ramachandran did the same with some of his own students. There are several instances when he told his students to publish papers just in their names even when they wanted Ramachandran as a coauthor on their paper.

Professor Mahindra Jain, currently at the University of Delaware in Newark, once asked Ramachandran if there was anything he was sorry about. He thought for a few minutes and replied that personally he was not sorry about anything, but he was sorry for his students who could not and did not fully use him. One of his greatest regrets at the Indian Institute of Science was that he had no interactions with other students and faculty members in other departments. Many new students at the MBU had heard that Ramachandran was a man of extreme moods, very short tempered and not very congenial in social visits. Nothing could be further from the truth. When some students did cross the barrier and paid him a visit in his house, it was inevitably one of their most memorable experiences. He was very kind, he listened to them, he talked to each one of them about their research problems, made appropriate comments and suggestions, and made them feel very important and very comfortable. More recently though, it is somewhat difficult to follow the conversations because of his speech difficulties; visiting students have left convinced that they were in the presence of a very great scholar, almost a saint.

Ramachandran was a gifted speaker and a superb teacher. It was a pleasure listening to his lectures on any topic—the structure of collagen, special forms of Fourier analysis, protein structures, the philosophy of science, or whatever. He never took a lecture for granted, he prepared meticulously before every talk, deciding exactly what to present and how to do it. Very often the audience did not have to know anything about the subject matter that he was talking about; he had a remarkable ability to lead them through the subject in a methodical fashion. There were no ambiguities in his presentations.

His unique ability to present highly complicated concepts in extremely simple words was such that even a high school student could easily grasp what he was saying. He explained the structure of proteins and the stereochemical conformations to John Kurian, who is currently a leading scientist in the field at the Rockefeller University in New York. This happened just after John had graduated from high school. It made such a lasting impression on him, that he decided to become a structural biochemist.

Everyone seemed to agree that what Ramachandran needed was a public relations person, an image-maker. He did not seek or desire to manipulate any political power; he was one scientist who did not know any politicians. Mr. Shankar Dayal Sharma was the President of India when Ramachandran was in Bangalore. President Sharma was a graduate student in Cambridge in 1947 at the same time as Ramachandran and they shared the same residence hall. Ramachandran never made any attempt to meet Sharma, and never capitalized on their university connection to seek political influence with the President of India. In spite of all the gossip about Ramachandran and the Nobel Prize, he says he never thought of getting the Nobel Prize, nor did he think that he was doing work of Nobel caliber.

Both Rajam and Ramachandran believe in Hindu ideology, but they are a totally non-religious family and neither believes in performing any rituals normally associated with the Hindu religion. Ramachandran's father was a strictly religious person and performed a daily "Pooja," a traditional ritual of worship performed by an orthodox Brahmin. Whenever Narayana Iyer had to be away from home attending various meetings, he usually delegated the responsibilities to his eldest son, Ramachandran, therefore became familiar with how to perform the ritualistic worship. Once Ramachandran left home and set up his own residence, he gave up all such practices. They did not perform the so called sacred thread ceremony that is normally performed by Brahmins for their sons when they come of age, somewhat similar to the bar mitzvah among the Jewish community. Their parents persuaded them to perform the thread ceremony for the sons as long as they were alive. It simply did not happen because both Rajam and Ramachandran did not believe in such practices.

However, every year they did perform the "Ganesh Pooja" and the "Saraswathy Pooja." The former is a worship of Ganesh, the elephant -faced God of Hindu mythology, who is believed to be responsible for removing all obstacles in various activities in life, such as moving into a new house or performing a marriage ceremony. The latter is a worship of Saraswathy, the Goddess of learning. This is particularly fitting as Rajam described their house as a "house of learning."

Ramachandran is a connoisseur of Carnatic music, the classical music of South India. He enjoys listening to old masters as well as the budding stars. Being a physicist, he not only enjoys the melody of the music, but also appreciates the science of it. His mentor Raman had published several classic papers on string and percussion instruments and Ramachandran no doubt absorbed some of that curiosity.

There is one more gifted aspect of Ramachandran, not known to many of his friends and colleagues. Ramachandran is a poet and has written nearly two dozen poems on topics including Linus Pauling, Walter Kauzman, science, religion, philosophy, and the Upanishads. The poems are an honest and spontaneous expression of his views and feelings and make a fascinating reading. They are all collected and reproduced in an Appendix at the end of these chapters.

Ramachandran can never sit idly or let his brain take rest; he is always thinking about some problem, trying to work out solutions, be it in crystallography, biophysics, philosophy, or music. In fact, this may have been a major problem in his life. He simply does not know how to relax. He spent a considerable amount of time attempting to prove Fermat's last theorem, and tried to provide conclusive proofs for the so-called four-color theorem.

He becomes excited and ecstatic while describing the results of his work or talking about science to others. This became very clear in one of my recent meetings with Ramachandran. I asked him a simple question: How would he like to be remembered by the readers of his biography? Instead of answering my question, he said that he had lots of other things to talk about and spoke of many unrelated things for the next fifteen minutes. He talked about the Klein-Gordon equation, Schrodinger's equation, relativistic quantum mechanics, electron proton interaction, Boolean algebra, π mesons and μ mesons, Bohr, de Broglie, Heisenberg, and on and on and on. I simply could not interrupt him. His thought processes were disconnected, incoherent, and unrelated. At one point he himself said; "I am thinking of too many things."

He went on to say how he had spent a considerable amount of his money in mailing papers that contained some of his ideas and results to people like Dirac, Feynman, and other famous nuclear physicists both in India and outside. None of them accepted or recommended the papers for publication. I suggested that part of the reason may have been that he was better known as a molecular biophysicist rather than a nuclear physicist and he responded by saying that even some of Schrodinger's results were not accepted while he was alive. Continuing this discussion, he said: "My psychological condition was forced on me by some of my fellow scientists. I could not find any postdoctoral fellow to work on any of my ideas." He got very excited when he talked about his relations with other scientists.

Finally, he answered the question that I asked him at the beginning. How did he want to be remembered by the readers of his biography? He said he wanted to be recognized as an intelligent person who came from a family in the middle strata of society, a family where education and learning were of the highest importance. His two brothers studied chemistry and engineering. All his children obtained doctorates. Was their any doubt that this was a highly intellectual family?

Rajam aptly described her husband in two simple words, she said that Ramachandran was always a "tormented individual." He worried about everything. If anything did not go according to his view of the world, he worried about it. Some of his frequent complaints were that he was not getting a fair chance, his merits were not being appreciated, and his work was not being recognized, neither by his colleagues in India, nor by scientists in other countries. He had to fight an uphill battle at all stages, whether it was publishing a paper, purchasing a computer, or making administrative changes requiring a postgraduate diploma before a student starts doing research.

Mrs. Ramachandran recalled a conversation she had with Professor Chandrasekhar, the Nobel astrophysicist from the University of Chicago. She had asked him why he did not return to India after the death of his uncle Sir C. V. Raman and take over the directorship of the Raman Research Institute. He apparently replied: "I have not accepted fully the American way of life, the Americans have not fully accepted me or my way of life. However, I felt that I would be a greater misfit in India than I would be in the United States. I feel that the directorship of the Raman Research Institute is not a right of the members of Raman's family."

Mrs. Ramachandran felt that as an experimental scientist her husband was a greater misfit in India than Professor Chandrasekhar was and yet he courageously faced the situation and stayed on in India even when he had several opportunities to work at universities in the United States and Europe. Professor Harrington of the Johns Hopkins University wanted him to come to Baltimore; he got a job offer from the University of Florida in Tallahassee; and the Pasteur Institute in Paris wanted him to start a molecular biophysics department there. Ramachandran decided to stay on in India despite all the tribulations and disadvantages.

Even in India, there were much greener pastures for Ramachandran but he did not take them. When Professor Sir K. S. Krishnan retired as the director of the prestigious National Physical Laboratory in New Delhi, Jawaharlal Nehru, then prime minister of India, wrote to Sir A. L. Mudaliar and asked him to convince Professor Ramachandran to take the job. Mudaliar, of course, left it to Ramachandran's discretion, who had a frank discussion with Sir K. S. Krishnan about working at the NPL. He became convinced that the director's role was simply that of a showpiece and that it would not be easy to conduct research in such a politically charged appointment.

Ramachandran stayed in Madras and later in Bangalore; that is something notable that no Indian should ever underestimate. Even simple disabilities are a big disadvantage in India. Certainly Indian society has not fully grasped the implications and complications of mental illness and psychiatric problems. At least that was true when Ramachandran was coping with his mental problems.

Undoubtedly, Ramachandran had his problems. He certainly had difficulty relating to others. His ego did not permit him to easily accommodate lesser mortals than himself. He would not and could not tolerate what he considered incompetence, inefficiency, or dissension. Right from the beginning, he had been told that he was brilliant. No doubt he was head and shoulders above many people who surrounded him; people told him so. The more he listened to such praise, the more he began to believe it and to feel that everyone should listen to him and agree with whatever he said. He could not easily tolerate criticism.

Early on, as Vice Chancellor of the Madras University, Sir A. L. Mudaliar allowed Ramachandran to have his way; it satisfied his ego and it worked well for everyone concerned. When Sir Mudaliar left and Mr. Sundaravadivelu came to power, things began to change. Admittedly, there were disagreements on fundamental issues. However, their personal egos played an important role in Ramachandran's decision to leave Madras and go to Bangalore. Some believe that same ego was the cause of his leaving Bangalore to go to Hyderabad.

In any event, Ramachandran has immortalized himself in the field of molecular biophysics and protein conformations. Every new protein structure determination is accompanied by a calculation of the Ramachandran plot. Compliance with the original limits for phi and psi imposed by Ramachandran and Sasisekharan is still valid after nearly thirty-five years. Ramachandran is easily the best biophysicist to come out of India. We all should be proud of his achievements.

23. Epilogue

Since the previous chapters were completed, Ramachandran and his family suffered a terrible tragedy. Mrs. Ramachandran, the beloved Rajam to all who knew her well, suffered a massive heart attack and passed away on 3 July 1998. The shock of the tragedy and the consequences of this terrible loss have not yet been completely realized by Ramachandran or his family. Ramachandran and Rajam had been married for nearly fifty-three years and they depended on each other. For Ramachandran, Rajam was an inseparable companion.

In 1997, they had closed their residence in Bangalore and moved to Ahmedabad, in the state of Gujarat in North India, to be near their son Hari and his family. It must have been an agonizing decision for both of them because they had spent all their life in South India, mainly in Madras and Bangalore. They liked the moderate climate of Bangalore, and became used to the cultural and intellectual environment there. By Bangalore standards, they had a reasonably large and comfortable house that provided ample accommodation for themselves and their children whenever they visited.

By the time I interviewed him for the book, the Parkinson's disease had almost completely paralyzed Ramachandran. He required the help of a walker to get around and rarely went anywhere outside his house. Physically disabled persons have a very hard time getting around in India and Ramachandran was no exception. There is no convenient mode of transportation for someone in a wheelchair and adequate facilities are not available in buildings. He needed assistance to walk in his own house and perform his routine activities. Rajam's presence was absolutely indispensable; she performed all the routine household chores.

Ramachandran had hired secretarial help in Bangalore. Because his disability had not stopped him from thinking and writing, he would dictate his letters and notes to his secretary, who would type them for further action. I had the unique opportunity of spending several hours every week talking to both of them. In the last few months, though, Ramachandran's speech was slightly slurred and very often Rajam would reinterpret them for me. She would also help him to recall various dates and events in their life. It was an absolute pleasure to listen to her erudite comments and answers to my questions. She was immensely helpful in compiling the information to write Ramachandran's story.

Rajam suffered from high blood pressure and was often worried that if something were to happen to her in Bangalore there would be no close relative who could care for Ramachandran. Their oldest son, Ramesh, and his wife were in Boston, their daughter, Vijaya, was in Austin. Only their youngest son, Hari, remained in India. He was a senior research scientist at the Plasma Research Institute in Ahmedabad in North India and so the Ramachandrans decided to move there in 1997. They stayed with their son and his family until they bought their own apartment. The climate in Ahmedabad is brutally hot most of the year and the language spoken in that region is Gujarathi, very different from the Tamil that the Ramachandran family spoke at home. There were no close friends or scientific colleagues in Ahmedabad. But clearly the compensation was their proximity to their son and his family. In particular they enjoyed playing with their only grandson, who was a very happy, playful, smart three-year-old. They derived hours of delight being with him.

Rajam was an absolutely delightful woman—always smiling, jovial, courageous, and extremely knowledgeable for someone who did not enjoy the benefits of sophisticated college education. She accompanied Ramachandran on most of his trips outside India. She was an integral part of all the trials and tribulations in Ramachandran's life. She took good care of him during his unpredictable psychiatric problems, and she kept their family together, preserving their confidence and morale, especially at the time of the children's formal education. Ramachandran, of course, was totally dependent on her, particularly after the onset of his Parkinson's disease. Toward the end, she was also his secretary, writing his letters and other correspondence. Only time will cure the tremendous loss of such a dear person.

Her death was sudden, and has taken their family and friends by shock. Indian women consider themselves fortunate if they die while their husbands are still alive; the perennial red circle of *kunkum* that adorned her forehead was a traditional symbol of life with her husband. She passed away with that symbol untarnished.

Poems by GNR

1. Dedication
To my revered Guru
Professor Linus Pauling

Linus Pauling
Is a name to conjure with,
In chemical bonding
And whatever forthwith
Follows for all matter,
Both inanimate and alive
Their nature and character
And how they will behave.

His great alpha helix,
That opened the path
For the solution of structures
of all biopolymers,
Is a star that will adorn
The firmament of Science,
For it has revealed to biologists
Completely new ways.

As a submission to this master,
I have today
Prepared a short paper
Following his way
Which shows that his conjecture
On Vitamin C
Is surely a true picture
Of what is expected to be.

2. Unchangeable Space and Time in Relativity Theory
Dedicated to Professor Panofsky

Theoretical Physics, O' mathematical physics,
Why should you put me in such a fix?
The ideas are so simple;

But what a big jumble
Do you make of those simple z,y,t and x?

They are there for all to see and handle,
How can they change from example to example?
It is true they can transform
From platform to platform;
Only because you refix the clocks in each example.

Lorentz transformation is the basis of physics;
But there is nothing mysterious about it for lyrics.
That the velocity of light
Is independent of flight
Is a fact of observation, and not of mathematics.

The invariance of the interval 's in a theory,
And the covariance of four-vectors a fortiori,
Are but simple formulae,
Though powerful their sway,
To make the check of theory in physics so easy.

By all means, use mathematical equations high flown,
To reveal relations that, otherwise, are not so well known,
But remember they are encased
And, on solid physics, based,
And formulae are but fuel for the rocket to the unknown.

3. Molecular Architecture of DNA

DNA has a crucial function
In genetics and metabolic action,
Watson and Crick
Said it is a twisted stick,
Having throughout right-handed torsion.

Biologists have puzzled faces,
How can it go through the paces
Without offending
Basic grammar of topological cases ?

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Ram and Sasi said DNA might
An alternating helix be, half left, half right,
The chains fall apart
As H-bonds do part,
And there is no trouble of tangling fright.

What is the theory of the alternations?
Ramesh said they come from confabulations
Of opposing forces,
Which have resources
To produce reversible of twisting rotations.

* Are the two strands of cellular DNA
Twisted around, or only side by side?
We must await
Some more results
From X-ray, ORD and other measurements.

(* This last verse does not rhyme, since
What it says is not final).

4. Polynucleotide Dihedral Angle Notation

Alpha, beta, gamma, delta
Epsilon, and then up to zeta;
Torsion angles, the main chain contains,
Ribose, or not, whichever obtains.

The first two are 'bout bonds at P,
Others then from five to three-prime P,
Across the sugar, with bond four-three C
In backbone path. Angles ring, below see.

With pentose ring twists, employ nu's
For that against O, number zero use,
Going to nu-four of the angle fifth;
For each index, find atom against ith.

Sugar-base torsion, chi it is called.

When O to CH cis zero is it equaled;
Named anti, for ninety plus minus this-
Syn der name when near one eighty it is.

In extras that occur, bound to sugar or base,
Use peptide rules, made to suit each case.
With angles others, use anything you like
As symbols or numbers, for convenience' sake.

5. Essence of Genetic Algebra

New Sutra: $AB = A + B$

Example: $(AB)^2 = (A+B)^2 = AA + 2\,AB + BB$

Commentary:

Mendel's AA is A alone,
That will give us one-two-one,
Ev'rything else comes from this one.

Ram amended Mendel's way:
AA is A plus A,
And AB is A plus B,
Mix them up as you like (it) to be.

The new sutra is an algorithm;
It can fit into computer rhythm,
It shows how to prevent diseases,
That do arise from genetic causes.

6. Enzyme and Energy

Enzyme, enzyme, what are you?
Living catalyst, in my view.
If you do not exist now,
How will there be life anew?

Chemical changes can take place

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Because of you, at decent pace,
Leading to life's subsistence,
At heat levels in existence.

Molecular biologists
Require help from biochemists,
So that they may imitate
Life's mystery on the plate.

Cellulose from sunlight is,
In plants, formed by synthesis,
If we turn the process back,
Energy surely we can pack.

7. The Expert and The Common Man

Dedicated to my revered friend Professor Walter Kauzmann*

To be an expert is the hope
of any who is a scholar's isotope;
The common man is without hope
In this arena, full of high-flown dope.

The expert with authority, sure asserts
That what he says is always certs,
Who are you to question my words,
When you do not know all the charts?

But this expert, alas, surely ignores
anything not connected with his mores.
What does it matter if A or B is close?
He cares only for X,Y,Z, - his homes.

The common man-he everything sees;
although, about nothing, the limit perceives,
He would like to pass through his sieves
The organic whole, not dissected pieces.

Of course we always need the expert
To organize, and process, the required effort

To illuminate Nature's darkest part;
But let him not shroud the whole import,
Of the philosopher's view of the complete court
By demands undue of his deep, but little, part.

The human mind quite often does find
The expert's dishes, though of the choicest blend,
Tasteless, if not mixed, with the kind
Of broad-based vision that the seers can find.

So, if you find the results of your effort
Lead to knowledge that gives you comfort,
But dead against what says the expert,
Wait; more thought will soon produce rapport.

Let the experts address the common man,
And make clear at once their whole domain;
Then they who disagreed will all exclaim
"We have no disputes," with full acclaim.

I love those experts,
Who give their purports,
Without props and supports,
In brief words, sharp shots.
They give all comforts
For one to go forwards
In deep search for truths
That gladden all hearts.

* " I am skeptical of everything until I can derive it myself" Kauzmann in personal conversations with the author.

8. Cancer and its Cure

DNA chains are the essence of life;
They must double when the juice is rife.
How this starts, and when they will do part
Are two problems that are miles apart.

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The mechanism of chain separation
Is partly based on base continuation;
Also rests on super helix formation,
Which gives a means for its initiation.

I do know this is of importance —
The concentration of the right components,
That loosen the base pairs and make additions
Have to be right to start duplications.

If juices lie low, cells don't divide;
By feedback regulation, these are rightly made.

Make these wrong, and you have proliferation,
And unregulated growth, in great profusion.

If we can find out what leads to constancy,
We can, safe and sure, control malignancy.

9. Superhelical Twisting and Replication of D N A

The Problem: Is super-heli-cal- twisting,
Extra over the net twisting?
Or, is it all the twisting
That is, over no net twisting?

Of the two specifications,
Which can suit the functions,
Of D-N-A replication,
And also of recombination?

We get facts of pure genetics
As a result of chemical physics,
Via a mixture of Biochemistry
And a dash of physical chemistry

The Solution: But what really is the fix
Is that aspects of mathematics,

Such as topology and chain geometry,
Upset the safe rules of symmetry.

On whom will you rely more,
Mathematician, or physicist of yore?
Mix up energy minimum with topology
Can you explain all of biology?

Come, come, don't you despair!
If you find theories don't compare,
There must come soon a meeting point
Of both point and counterpoint.

September 16, 1978

10. How to Give a Good Lecture

Plan your lecture in content and sequence;
You need not bother about the style of each sentence.
If your ideas are always precise, sheer,
Would your language not be sharp and clear?

11. How to Solve a Problem

If a problem is clearly formulated,
Would it in no time, not be decimated?
The real job is the full description;
Then experts can always find the solution.

12. Knowledge and Wisdom

What is Science,
If not knowledge,
Pure and simple,
Of things around us?

Kasthvam, Koaham?
Kuta aavaatah?
Kaa me janani?

Koa me taatah?*

Who are you? Who am I ?
Whither come ? Who is
Your mother, your father
-from Sankaracharya's
"Bhaja Govindam"

What is this ?
Whence come it ?
Who produced it ?
Who controls it ?

How can we know
All about it
If we not enquire
How we know it ?

Can we know
All of Nature?
Run it of itself ?
Or can we amend it ?

Wonders never end.
We only nibble it,
The fruit of knowledge,
Know it and be wise.

November 1, 1978

13. Exponentiation of Knowledge

Two into two will make it four,
Put into it twos four more;
This expands it into sixty four.
If you put still twos four more
Grows it huge to ten twenty four;
Exponential it swells with bits ever more.

Knowledge is like this, as one can tell;

One more factor makes it twice to swell;
Ten new data need thousands to quell,
And coordinate well, not leave pell mell.
Hell is as well for a scholar to dwell,
If heavenly bell only rings bits at will.

A hundred years ago, one could hope
To claim acquaintance with all the dope,
That was there in the Library of the Pope;
But it is a labor today, to climb the rope,
Herculean, indeed, even if it is the hope
To reach the top of a single field aprop.

Specialists galore
Now come up ever more;
They climb ashore,
Tiny islands to explore.
Their rich pastures
Are indeed pleasures,
To fill the measures
Of mind's great treasures.

But, there exists the need,
For other men indeed,
Who can clarify this feed
Into a sparkling bead.
Many beads as these
Make garlands that please;
Makes knowledge at ease,
And minds rest at peace.

January 3, 1979

14. Measurements of Science - The essence of all Science

Number, number, number;
All is expressed as number —
Be it the weight of timber,
Or hours of soft sweet slumber.

Studies of problems in research
Are made of relations we search
Between numbers that form the torch
That light the ideas we preach.

Mathematical formulae in symbols
Delicately poised as in gimbals
Are great. But as in thunder it rumbles
If converted to numbers, in examples.

Take one imaginary conjecture;
Deduce from it a new picture —
That forms a standard lecture
Of many a theoretical structure.

Such theorists never seem to care
If premises with number do compare,
Of the subject, which they prepare
For an intellectual feastly fare.

Equations and formulae sure abound
In their pulsating theoretical fund.
Beauty of their structure is their main hunt;
Numbers to them are but lowly bound.

Of course, I must surely admit
Not all theorists behave thus; to wit
Applied mathematicians try their bit
By formulations, their real target to hit.

But I do not understand physicists
Expanding on little like lyricists;
Not predicting, as required of analysts,
But going round, as in acrobat's twists.

If they try to computerize
Every equation which they theorize,
Great enlightenment will be the prize—
Clarity and acceptance, of immense size.

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Instead of forming a mutual admiration society,
If mathematical physicists would only seek sobriety
of the bench scientists, and talk to them, not in pity,
But in equality- would we not have a unique moiety? *

The error that is common with all such theorists,
Be they of race physicists, or even pure mathematicists,
Is that they delight in cyclic and thought gymnastics,
Never caring for ground numbers, which form the acrostics.

I say all theorists should learn to make calculations
On an abacus, or slide rule, or via manipulations
Made on electronic digital computers. Then, predictions
Would make sense, and science rise to greater elevations.

* "In my view, such more complicated systems and their combinations should be considered only if there exist physical-empirical reasons to do so."

-Albert Einstein in "The meaning of Relativity "
Sixth edition, 1956, page 156.

15. MANAS* And MAATRAA+

(* = Mind, + = Material world, matter)
Logic, logic, logic
Nothing strange, like magic;
Think straight and deduce
Then are ever true, your views.

The rules that logic follows,
Always there for all fellows;
No need to state in symbols;
Valid ever, if pure mind gambols.

What if theorists hard assert
That logic is like a desert,
That many paths just peter away
And no structure has ever full sway.

Theories in physics only connect
A set of data with another fact.
If life must ever have impact,
Such connections are sure compact.

Science is based on observation
And also logical deduction.
Assume God-given senses and the mind
Are enough, for all its laws, to find.

This means that we can never accept
Completely, theories that have any defect
Working hypotheses, surely they are;
But Laws of Nature, they never are.

Man learns, anon, ever more and more
Of beauties of Nature, lying ashore,
Jump the ocean if you wish, like Hanuman,
But never falter from commonsense, human.

October 22, 1978

16. Knowledge has no end

In the end, there is an end;
This is true of the wonderland
Of every branch that is dependent
On all others, to make a pendant
Of wisdom, that is resplendent
With beauty; yet truly concordant
With the kavi's* sight of the true anant+.

Anadyantax is the picture
That comes up in every lecture
On reality, Truth and Nature.
One can but conceive the feature
In general terms, not in miniature;
Deeper you go, farther the pasture;
Meditate; and it shape your culture.

Art, Science, Logic, Philosophy,
All are, of Nature, only a copy.
If both in and out, you are happy,
Dream on, treat it as your baby,
Pleasantly dance; caper like a puppy,
With sure thoughts that need not be apty,
But close to reality, and never crafty.

As said before, it will never finish;
"Art is long", whatever your wish;
"Time is fleeting", true but your cash
Pass on to others, you can, for fresh
Outlooks and approaches. If the fish
They catch is as simple and fresh,
We can have, indeed, a wholesome dish.

* Kavi = poet

+ Anant = without anta, or end, unbounded.

x Anadyanta = Without a beginning or an end;
picture of Atman, or Ultimate Reality in Hindu Philosophy.

November 1, 1978

17. Anoaranooyan Mahato Maheeyaan
(Smaller than the smallest, larger than the largest.)

Paradox of the Paramaathman

Is all this there by chance ?
Or by sheer necessity ?
Is there a guiding force ?
Or does it evolve by itself ?
The answer is simple, but strange -
"All these, at the same time."

The guiding force
is itself the guided.

It runs everything —
But is, itself, all of it.
HE is omnipresent;
Omniscient, omnipotent.
Nature's Law is God's hand;
No! Nature is the Universal Truth.

That is the paradox.
He is nowhere to be found;
Yet He is everywhere.
Seek, and ye shall find!
Seek where ? Inside, outside ?
Yes, He is both within and without.

Can IT be both cause and effect ?
Isn't one before the other ?
You can't ask such questions.
In that place, all is same —
Before, after, behind, in front,
Up, down, all merged in one.

Undifferentiated,
Infinitely varied,
Particle and wave,
Matter and light,
Energy and essence,
Space and time,
White and black,
All one, all equal,
If you can but perceive it.

Eyes cannot reach there,
Nor ears, nor any senses,
Not even reason, not mind.
Only true devotion,
Unmixed meditation,
Merging with all
Yet away from all,
Seeking the unknown

Not here and there,
But all within you,
Antaratman is Paramatman

November 1, 1978

(GNR had separately marked this poem, I asked why, he answered: It's my best)

18. Lamp of Criticism - Light of Progress

(Accept naught, if it fit not your thought)

To take a set of ideas, which are all in a tangle,
Separate them apart one by one, all single,
And put them right together, not in a jumble;
But to make a story, all from one angle;
Is surely a tall order, not easy to wangle,
Except for one sure of his way in the jungle.

If the postulates are valid, and clear the conceptions,
It is easy to make a number of deductions,
Without the need arising to make any corrections.
But, let some of the steps contain misconceptions;
Now hard it is to find the few exceptions,
And set right the faults, and avoid deceptions.

Theories there are, full of power at this moment;
But few that can stand the onslaught of new comment,
For they form only part of the train, a compartment,
And often consider the rest to be of no moment.
If you want the full train to move on without torment,
Grease all the wheels, and turn on, in full, the current
Of sobriety and tolerance; no matter how innocent
The critic is of debate; on truth leap the firmament.

You are ever the scientist
From birth, a true scientist.
If you ever can list

Things around you, and test
What is not, and is, best,
For life and all to exist,
How can you far subsist ?
So be brave and contest;
Take part in the inquest
Of past thoughts; to conquest
On ahead, ride abreast
New tides that hit the coast.

November 1, 1978

19 How to be a good scientist

(Dedicated to my friend V. Jagannathan)

Art, or science, is all the same;
Heart sincere is its real seed,
Bubbling thoughts, made calm and tame,
Form sculptured shapes, to fill its need.

If you wish to explore anew
Always avoid the beaten path,
Swinging ahead on avenues new,
Apply with zeal, brain, brawn, both.

However established a theory may be,
It has its limits, as many can tell.
Seeking its help is but all too easy;
But it need not have tones for every call.

Dissect your problem and take it to pieces;
Assemble it again with different connections.
A lane that was crooked, of a hundred paces,
Behold! is a short broad street, with no disjunctions.

To make a good portrait, true, of all subjects,
Never is it enough to look from one angle.
Go around it, absorb all its aspects;

The picture you draw will sure make one tingle.

November 1, 1978

20. Logic and Reason

The rules of logic are neat and brief —
Use "and" and "or" and "not" and "if"
All arguments require only these.
Qualified, they need 'all' or 'some' apiece,
And whenever needed, 'none' at all.
They help make discourses, at beck and call.

Implication is needed most of all;
'If A, then B' vital step for all
Arguments employed in real life,
Or for proofs in maths, written in brief.
It only works when fact A is true,
To lead to result that B is true.

Block diagrams, we know, make it clear
What steps are needed, from far and near;
A flow-chart is always the prerequisite
For a full scale program to be exquisite.
If thought flow is marked, as for traffic,
With symbols clear, resound it will with logic.

Logic is the basis of knowledge all;
Of science, of religion, of art and all.
If scientific knowledge, developed and wise,
Is employed to explore, and open, price,
The esoteric secrets of logical thought,
Reassured it makes Jnana, Vijnana, and aught.

'God is reason', say the vedas of old.
If man can but think out, brave and bold,
And attack the unknown, using the known,
In no time at all, Vidya new will he own;
Unlimited his success, whatever the issue,

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Truth the goal, he fails not to pursue.

21. Expansion of Knowledge

That all that glitters is not gold
Is as true of science, as of trinkets sold;
Only intensive search will make unfold
Knowledge supreme, lit by lamps of old.

Two ways, there are, of expanding the known -
Proceed along pathways already known,
Or make a leap into the seas unknown
And distill from it with methods yet to be known.

The first is easy, although rather arduous;
The results are assured, and of value, copious;
But its success, to reveal, is rather dubious,
New avenues, that clearly, are not obvious.

'Asa tho maa sadgamaya' is the saying bright,
Of the second way - " Lead me from darkness to light."
If followed right, it leads me to the mightiest height.
Needs it, however, the employment of great insight.

By whichever way you descend into a valley near,
There is no path other than to the bottom, dear;
But, ascend the mountains, go away from here;
The rivers there take you to the vast ocean clear.

Knowing too much of accumulated knowledge
Can be a hindrance, not an adi, for the bridge
Which you are building right across the gorge.
A fresh mind is what makes new ideas emerge.

If you feel something is not quite all right,
Do not read learned treatises up till night;
Rapidly scan through popular articles, bright;
Absorb, ponder, meditate, and get new light.

Be a good boy, or a girl, as you may be;
Think of science as a game, or puzzle, may be.
Whether you fail, or succeed, as it may be,-
No matter- enjoy the hunt for what it may be.

22. Science and Society

Science for the Nation

I say, our scientists, their passion
For discovery and new creation,
Should blend, with the real devotion,
To the vast needs of the Nation.

Scientific ideas, pure and simple,
Laws of nature, for example,
Are enough for some, pure, humble;
But they alone are not ample.

Many are needed to undertake
Studies practical, and partake
In Nation - building, and to make
Food, Home, Drugs, Dam and Lake.

They would then have achieved
Satisfaction never perceived;
Since real truth is conceived
Only in Karma truly achieved.

March 1, 1979

23. To Our Scholars*

In the spirit of the don,
Work must go on and on,
Teach what you know in fun,
To all, as you will your son.

You can never abandon

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This duty, as a burden;
Your devotion, to our nation,
Donate, in renunciation.

November 1, 1978

*We teachers and researchers will gain respect only if we keep the practice of our profession far above and apart from the mundane part of our lives.

24. Tame the Mechanical Demon

Who first made the machine go ?
Of course man, a long time ago,
With the potter's wheel, bow and arrow,
That set the age of invention glow.

Ever since, has man attempted
To tame Nature's Laws as he wanted;
Make sure help whenever needed
To construct things, as the pyramid.

For centuries and millennia,
The fire of invention blazed on;
Gadgets and devices grew anon;
Today we have a million and one.

As writers and philosophers foresaw,
The common man who looks with awe,
At devices that cut, cook, and sew,
And also run, fly, plough and mow.

The latest one that has arrived
The computer, von Neumann devised;
Can do things, that before required
The use of brains and power of mind.

It can solve problems, run machines,

Fly a plane, or play with games.
Is it a monster that will replace
Man, as the ruler of earthly space?

On throwing a switch, it can release
A guided missile that flies through space
And control, direct it on space —-
A demon created, for man to face.

Computers will fight wars in future;
Relentless they are in nature;
From sealed instructions, they never waver;
Nor think of right and wrong, for ever.

Can we control this Frankenstein,
Tame it to be a friendly slave?
Of course we can, if we ourselves
Promise to use it only for good.

Good, or bad, is but man's choice.
Why can't we all shout with one voice,
That these devices coming one a day,
Will only be used in a friendly way?

What wonderful things can it not give?
Tingling music, art, designs and all
That delight children, and grandpas alike;
Also creators, in their flights of fancy.

Let us then be up and doing,
Choose the way of all well - being,
Only make machines, that clear the way
For a life chock full of fraternity.

September 5, 1979

Kena Upanishad
Greek Alphabet for Logic

Alpha, beta, gamma, delta,

Epsilon, and zeta,
Years gone unaccepted for
Nucleic acid data
But I find them good matter
To fill in the quota
For symbolic logic in computer
And automata.

Alpha and beta form twins
For all terms in logic;
One, zero; zero, one; stand for
Yes, no, made cryptic.
One, one; and nil, nil; are the parts
New, of the fabric
That makes up the code, in maths,
Of thoughts serene and comic.

Connectives join terms to make up
All types of senses;
One for if, then and two for
Likeness and differences;
Four more for use with "or", and "and",
"With", "upon" nuances;
These form the basic stock for
Logic of sentences.

These suffice for saying yes or no,
Or I don't know;
Or when parts of an argument disagree,
To stop its onward flow;
But if you need discuss the rules re
Thoughts of long ago,
Like "There is no smoke without fire".
Further on you must go.

Reasoning like these, with "there exists"
"For all", and "for none";
Want you to say when such a sentence is true,
Or truth is gone;

You need the lamps of zeta, gamma,
Delta, epsilon,
To demonstrate to others, ideas
Known to you alone.

All knowledge needs precision; words
And sentences must shine;
They cannot do so unless there is
Logic, clear and serene;
Commonsense, some say, is enough to
Check what thinkers opine;
But the purity of algebra is what will
Make thoughts refine.

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APPENDIX 1

Summary of Ramachandran's career

Gopalasamudram Narayana Ramachandran
Date Of Birth: October 8, 1922
Spouse's Name: Rajalakshmi (deceased June 3, 1998)

Father: G.R. Narayana Iyer
Mother: Lakshmi Ammal

Children:
Dr. Ramesh Narayan,
Prof. of Astrophysics,
Harvard University

Dr. Harishankar Ramachandran,
Senior Scientific Officer,
Institute of Plasma Research,
Gandhinagar, Gujarat

Dr. Vijaya Ramachandran,
Professor of Computer Science,
University of Texas,
Austin, Texas

Education:

1939 - 42 B.Sc(Hons) Physics, St. Joseph's College, Trichy
1942 - 44 M.Sc. Physics, Indian Inst of Science Bangalore (Under Prof. C.V. Raman)
1944 - 47 D.Sc. Physics, Indian Inst of Science Bangalore (Under Prof. C.V. Raman)
1947 - 49 Ph.D. Crystallography, Cavendish Laboratory, University of Cambridge, England (Under Prof. Lawrence Bragg)

D.Sc. (Honorary) Roorkee (1978) IIT (Madras) (1985)
Hyderabad (1989), Banares (1992)

Professional Occupations:

1984 - 1989 INSA Albert Einstein Professor, Mathematical Philosophy Group, Indian Institute of Science, Bangalore
1981 - 1984 CSIR Distinguished Scientist, (Available in any Part of India)
1978 - 1981 Institute Professor, Mathematical Philosophy, Indian Institute of Science, Bangalore
1971 - 1978 Professor & Head, Molecular Biophysics Unit, Indian Institute of Science, Bangalore
1967 - 1978 Part-time Professor of Biophysics, University of Chicago, Chicago
1969 - 1971 Jawaharlal Nehru Fellowship, University of Madras, Madras, India.
1962 - 1970 Director, Center for Advanced Study in Biophysics & Crystallography, University of Madras
1952 - 1970 Professor & Head of Dept. of Physics, University of Madras, Madras.

Membership in Professional Organizations:

Fellow of the Indian Academy of Sciences (F.A.Sc.)
Fellow of the Indian National Science Academy (F.N.A.)
Fellow of the Royal Society of Arts, London (F.R.S.A.)
Fellow of the Royal Society, London (F.R.S.) (1977)
Founder Member, Indian Academy of Yoga
Founder member of the Third World Academy of Sciences
Hon. Member, American Society of Biochemistry & Molecular Biology
Hon. Foreign Member, American Academy of Arts & Sciences, Boston
Hon. Fellow of the National Academy of Sciences of India, Allahabad
Hon. Fellow of the Indian Institute of Science, Bangalore

Memberships in Community Organizations:

Member, Board of Scientific & Industrial Research, Govt. of India, (1962-65)
Chairman, and/or Member, National Committee for Biophysics,

(1967-1976)

Chairman National Committee for Crystallography (1963-1970)

Member, Council of International Union of Pure & Applied Biophysics (1960-1972)

Member, Commission on Macromolecular Biophysics of IUPAB (1969-1974)

Member, Various Sub-commissions of the Commission on Biochemical Nomenclature of the IUPAC-IUB (1966-79)

Editor Current Science, Bangalore (1951-57)

Member, Editorial Advisory Board, Journal of Molecular Biology, Cambridge (1959-66) (From Inception)

Member, Editorial Board, Biochimica et Biophysica Acta, Amsterdam (1965-72)

Member, Editorial Board, International Journal of Peptide and Protein research, Copenhagen (1969-79) (From inception)

Member, Editorial Board, Biopolymers (1973-83) (From inception)

Member, Editorial Advisory Board, Journal of Biomolecular Structure and Dynamics (1983-) (From Inception)

Member, Editorial Advisory Board, Connective Tissue Research (1972-) (From inception of new name)

Member, Editorial Board, Indian J. Biochemistry and Biophysics and several other Indian Journals

Prof. Ramachandran has worked in a number of fields in Physics, Chemistry and Biology and has contributed more than 250 publications and several reviews in well known international journals. His main achievements are the following:

1. Early Studies:(1942 - 1952)

Among the studies in this early period, may be mentioned his work on x-ray topograph of diamond which gives a picture showing the variation in perfection over the surface of the plate of the crystal. Publications in 1944-46 were probably the earliest application of x-ray diffraction to delineate the variations of perfection in crystals in a photographic manner. The name topograph for such pictures appears to have been coined and adopted for the first time in these papers.

During this period, he was also probably the first to calculate the optical rotation of a crystal from theory, namely of quartz and sodium chlorate from their crystal structure. In his post doctoral work in Cambridge, he was associated with Dr. Wooster in working out techniques for the measurement of diffuse reflections of x-rays and utilizing these for measuring elastic constants of crystals. These studies were also probably the earliest in which the Geiger Counter was used to measure intensities of x-ray beam of such low power.

2. X-ray Crystallography:

After returning to Bangalore in 1949, he devoted his attention mainly to crystal structure analysis (both theory and practice). He carried over these interests to Madras when he joined as Professor and the main topics of investigation are as follows:
a) Studies on crystal perfection and its variation by using polarized X-rays, along with the development of the dynamical theory, with special reference to x-ray antireflection (Renninger effect);
b) Measurement of Bijvoet inequality and utilizing this for solving the 'phase problem' in crystallography, a technique widely employed now-a-days;
c) Developing new techniques for obtaining the coordinates of the remaining atoms in a crystal structure for which partial information is available. Of the three syntheses (alpha, beta and gamma) that were developed the alpha synthesis is equivalent to the technique employed for image reconstruction in holography.

3. In 1954, he published along with his colleague Dr. Gopinath Kartha the triple helical structure pattern in the protein collagen, which forms more than 50% of the proteins in the human body (*Nature, 174*, 269 (1954)). This was immediately accepted and has been applied in biochemical studies and later in biology and medicine. Dr. Ramachandran is the Editor of two volumes on Collagen, contributed by International scientists - "Chemistry of Collagen, Vol I," Academic Press (1967) and "Biochemistry of Collagen", Plenum Press, New York (1976) (A.H. Reddy) and has contributed the chapter on the Molecular structure of Collagen in both.

4. His close acquaintance with biochemical molecules such as proteins and peptides related to collagen led him to seek a simple technique for

theoretically assessing the probability of different conformations of these molecules in biosystems. This led to the publication of a path-breaking paper entitled "Stereochemistry of Polypeptide Chain Configurations" in the *Journal of Molecular Biology, 7*, 95 (1963) (with V. Sasisekharan and C. Ramakrishnan). The graphical construction used there is now known in literature as The 'Ramachandran Plot' and it has facilitated the theoretical investigations of stabilities of biopolymers and interactions between different molecules in the living system. Ramachandran's groups in Madras and Bangalore have contributed much to the extension of these studies through various proteins to nucleic acids and polysaccharides.

5. His experience with x-ray crystallography in his early studies made in IISc in Bangalore under Prof. C.V. Raman and Cavendish Laboratory, Cambridge, under Prof. Lawrence Bragg had led to an intimate acquaintance with Fourier transforms and their applications to diffraction theory. In 1971, he applied these methods for giving the theory of Image Reconstruction from shadowgraphs (such as X-Radiograms) using the Convolution Technique. This was published in *Proc. Roy. Acad. Sci. USA 68*, 2236 (1971) (with A.V. Lakshminarayanan) This was the beginning of the studies made in various laboratories on various tomographic methods using x-rays, NMR imaging, ultrasonic image reconstruction and is particularly adopted for CATSCAN equipment which has contributed greatly to the development of medical diagnosis and surgery.

6. Since 1978, he has turned his attention to Fundamental Theory and Mathematical Philosophy. It led to the development of a new Boolean Algebra Vector Matrix Formation for computer manipulation of logical relations, which can be applied for the computer implementation of any logical argument. The essential principles of these were published in *Current Science, Bangalore - 51*, 625 (1982), *52*, 292, 335, & 341 (1983), *55*, 12,67 (1986). A number of research papers entitled MAT-PHIL reports of the Mathematical Philosophy Group in the IISc have been written. It is believed that this BVMF form of representing logic is of universal applicability to any system of logic just as Matrix Algebra is employed for universal application of group theory to any system.

Honors, Citations and awards:

1. Shanti Swarup Bhatnagar Prize for (Physical Sciences (1961)
2. Watumul memorial Prize in Biophysics (1964)
3. John Arthur Wilson Award by American Leather Chemist Association (1967)
4. Meghnath Saha Medal of the Asiatic Society (1971)
5. Srinivasa Ramanujan Medal of INSA (1972)
6. J.C. Bose Award of UGC (1976)
7. J.C. Bose Award of the Bose Institute (1977)
8. Fogarty International Medal of NIH (1978)
9. Indian Institute of Science Alumni Award (1979)
10. Sir C.V. Raman Medal of INSA (1982)
11. R.D. Birla Award for Medical Sciences (1985)
12. CSIR Golden Jubilee Award for Life Sciences (1991)
13. M.P. CSIR Jawaharlal Nehru Award for Sciences (1992)

Other Biographical Listings:
Hobbies and Recreations:
Indian and Western Music
Detective Fiction
Eastern and Western Philosophy

1. Who's Who in Science and Engineering (Marquis Publications) 121
P.O. Box 37, New Providence, New Jersey 07974 - 0039 USA

2. International Who's Who (Europa Publications, 18 Bedford Square,
London WC1B/3IN, UK
3. Who's Who 1994, 35 Bedford Row, London WC 1R/4JA, UK
4. Men of Achievements, International Biographical Center,
Cambridge CB2 3QP, UK

APPENDIX 2

Summary of Ramachandran's dissertation for Master's Degree from the Indian Institute of Science.

The first chapter deals with the nature and structure of the corona produced by a large number of particles distributed at random, e.g. lycopodium dust strewn on a glass plate. It is shown, theoretically and experimentally that the corona consists of a large number of sharp discrete images of the original source of light (assumed to be monochromatic). The statistical law of distribution of intensity amongst these images is deduced, and has been verified by means of photographic photometry.

In the second chapter, the transmission of light through a fog composed of particles suspended in a medium is investigated theoretically. It is shown that the extinction coefficient for a fog consisting of opaque particles is double that given by purely geometric considerations, the doubling arising as a result of the diffraction of light. Thus the results of Mallock and others are shown to be in error by a factor of 2. For transparent particles a theory is developed on the basis of a simplifying assumption that the wave passing through an individual particle suffers only a change of phase. The treatment successfully explains the colors observed in the light transmitted by the fog.

In the third chapter, a theory of the optical phenomena exhibited by chromatic emulsions as well as those observed in the Christiansen experiment is worked out de novo on the basis of the diffraction of light by a sphere immersed in a medium of nearly the same refractive index. Expressions are derived both for the intensity of the transmitted light and for that of the light diffracted in other directions. These are discussed in relation to the intensity and spectral nature of the light, and it is shown that the theory can satisfactorily account for the various phenomena observed by Sethi and Sogani.

In the fourth chapter the ideas indicated in the second and the third chapters are employed to develop a theory of the coronae due to water droplets. A discussion of the expressions obtained shows that the theory can, at least in a general way, explain some of the phenomena exhibited by such coronae, especially the central disc and the rapid changes in the ring system produced by small changes in the radius of the drops.

In the fifth chapter, the general electromagnetic theory developed by him and the others for the scattering of light by a sphere is considered, and a theorem is proved that if the sphere is non absorbing, the total scattered energy is equal to the reduction in the energy of the transmitted wave. The results obtained by the previous workers for the scattering and attenuation by particles having sizes within restricted ranges are compared with those given in the preceding chapters for the same ranges, and it is found that they agree, provided the difference in the refractive indices of the particle and of the surrounding medium is small.

In the sixth and final chapter the optical behavior of a periodically stratified medium is investigated and expressions are derived for the reflection and transmission coefficients of such a medium consisting of a finite number of stratifications. The particular case of Lord Raleigh in which the stratifications consist of parallel plates of equal thickness, is deduced from the general theory. It is found that the spectral sharpness of the principal maxima of reflection cannot be indefinitely increased by increasing the number of stratifications, since the width of the bend of reflection in the spectrum has a minimum limiting value, which depends on the reflecting power of the stratifications. A study of the limiting case, when the number of stratifications is infinite shows that the reflection is total in the region of the primary maxima, and that outside them the intensity of reflection falls down rapidly.

(This work was the basis of the first paper published by Ramachandran in 1942 in the Proceedings of the Indian Academy of Sciences, a Journal which published a number of his original contributions.)

The theory is also applied to the problem of reflections of x-rays by crystal planes and it is shown that Darwin's and Prins's results can be deduced directly from the general formulae. Attention is drawn to a not unimportant error in Darwin's formulae.

APPENDIX 3

Graduate (Ph.D.) students of G. N. Ramachandran. M.S. candidates (by research) are indicated with *. (period until about 1967)

1. Lonappan, M. (Thermal Expansion)
2. Chandrasekharan, K.S. (NaClO3/NaBrO3)
3. Raman, S. (anomalous dispersion/fourier syntheses)
4. Srinivasan, R. (statistics/crystal structure)
5. Sasisekaran, V. (fiber diffraction)
6. Krishnamurthy, E. V. (analog computing- Leelavati?)
7. Dweltz, N. E. (Chitin)
8. Venkataraman, S. (Optical Activity)
9. Parthasarathy, R. (Anomalous Dispersion)
10. Sarma, Raghupathy. (Statistics, Crystal Structures)
11. Rao, S. Thyagaraja
12. Mallikarjunan, M.
13. Ramakrishnan, C. (Stereochemical criteria of polypeptides)
14. Subramanian, E.
15. Parthasarathy, S. (intensity statistics)
16. Chandrasekharan, R. (joint with RS)
17. Laskhminarayanan, A. V. (joint with Sasi)
18. Sarathy, K. P.
19. *Ambady, G. K. (Collagen) and then independent Ph.D.
20. *Aravindakshan, (crystal structure)
21. *Ranganathan M. (Barium acetate (triclinic)
22. *Santhanam, M. S. (Calcification of Collagen)
23. *Anantakrishnan, S. (joint with RS)
24. *Ayyar, R. R. (joint with RS, MS or PhD)
25. C.M. Venkatachalam
26. Manju Bansal(Indian Inst of Science)
27. A.S. Kolaskar (Indian Inst of Science)

APPENDIX 4

Scientific Publications of G.N. Ramachandran
GNR Principal author (Co-author if present)

Molecular Biophysics:

1. Elements of Helical Structure of Collagen, *Current Sci. 23*, 349, (1954) (G.K. Ambady).
2. Structure of Collagen, *Nature 174*, 269 (1954) (G. Kartha).
3. Orients crystallization of inorganic salts in collagen, *Experientia 11*, 343, (1955) (G.K. Ambady).
4. Studies on Collagen - Part I: Structure of the Collagen Group of Proteins, *Proc. Indian Acad. Sci. A42*, 215 (1955) (G. Kartha).
5. Occurrence of Chitin in the epicuticle of an arachind Palamneus swammerdami, *Nature 176*, 557 (1955) (G. Krishnan and M.S. Santhanam).
6. Structure of Collagen, *Nature 176*, 593(1955) (G. Kartha).
7. Infra red spectrum and structure of collagen, *J. Chem. Phys. 23*, 600 (1955).
8. Structure of Collagen, *Nature 177*, 710 (1956).
9. Cylindrical lattice structure of collagen. *Archives Biochem, Biophys. 63*, 255 (1956) (V. Sasisekharan).
10. In Vitro calcification of collagen, *Experientia 12*, 340 (1956) (M.S. Santhanam).
11. Structure of Elastin, *Proc. Indian Acad. Sci. A45*, 124 (1957) (M.S. Santhanam).
12. Studies on Collagen Part II: Cylindrical lattice structure of collagen, *Proc. Indian Acad. Sci. A45*, 363, (1967) (V. Sasisekharan).
13. Modification of collagen and gelatin by chemical reagents, *Recent Advances in Gelatin and Glue Research*, G. Stainsby Editor, Pergamon Press, London 1957 p 32.
14. Study of molecular structure of fibers Part I, *J. Sci. Ind. Research A19*, 357 (1960) (V. Sasisekharan).
15. Study of molecular structure of fibers Part II, *J. Sci. Ind. Research A19*, 488, (1960) (V. Sasisekharan).
16. Analysis of x-ray diffraction patterns of helical structures, *Proc. Indian Acad. Sci. A52*, 240 (1960).

17. Study of molecular structure of fibers, "Proceedings of the Physics Conference and Symposium on Solid State Physics Bangalore" (1960) p 174, (V. Sasisekharan).
18. Structure of Collagen, *Current Science 30*, 127 (1961) (V. Sasisekharan).
19. Structure of collagen, *Nature 190*, 1004 (1961) (V. Sasisekharan).
20. Structure of fibrous proteins and polypeptides, In "Collagen" Edited by N. Ramanathan and published by Interscience Publishers, (1962) page 3.
21. Structure of collagen at the molecular level. In "Collagen" Edited by N. Ramanathan (1962) and published by Interscience Publishers, page 81 (V. Sasisekharan and Y.T. Thathachari).
22. Structure of feather keratin Part I Protofibrilar structure, "Collagen" Edited by N. Ramanathan (1962) and published by Interscience Publishers, page 147 (N.E. Dweltz).
23. Theory of optical rotation of the alpha helix and its absolute configuration, "Collagen" Edited by N. Ramanathan (1962) and published by Interscience Publishers, page 199 (S. Venkataraman).
24. The structure of Chitin, *Biochim. Biophys. Acta 63*, 307 (1962) (C. Ramakrishnan).
25. Stereochemistry of polypeptide chain configurations, *J. Mol. Biol.* 7, 95 (1963) (V. Sasisekharan and C. Ramakrishnan).
26. Triple helical structure of collagen, "Aspects of Protein Structure" edited by G.N. Ramachandran and published by Academic Press, (1963) Page 39.
27. Biological large molecules, *Trans. Bose Res. Inst.* 25, 4 (1962), page 145.
28. Stereochemistry of polypeptide and polysaccharide chain conformations, "Aspects of Protein Structure" edited by G.N. Ramachandran and published by Academic Press, (1963), page 121, (C. Ramakrishnan and V. Sasisekharan).
29. Conformations of collagen and other fibrous proteins, (*Abstracts 6th International Congress of Biochemistry*, New York, July 26 - August 1) 6 (2), 115, (1965).
30. Molecular structure of living matter, *J. Sci. Ind. Research 24*, 213 (1965).
31. Some aspects of the structure of collagen, *Proceedings of the Symposium International Sur Le Tissue Connectif*, France (1965), (V.

Sasisekharan, A.V. Lakshminarayanan and C. Ramakrishnan).

32. Structure of proteins and polypeptides, (Presidential address delivered at Physics section Proceedings of the Combined 51st Session of the Indian Science Congress, Part II), 1965, page 37.

33. Did life begin as a crystal? *Science Reporter (CSIR India),* 2, 282 (1965).

34. Stereochemical criteria for polypeptide and protein chain conformations, Part II, Allowed conformations for a pair of peptide units, *Biophysical Journal, 5*, 909 (1965), (C. Ramakrishanan).

35. Determination of the possible conformations of the residues linked in a polypeptide chain, *Biopolymers 3*, 591 (1965), (C. Ramakrishnan and C.M. Venkatachalam).

36. Refinement of structure of collagen, *Biochim. Biophys. Acta. 19*, 314 (1965), (V. Sasisekharan).

37. Molecular structure of polyglycine II, *Biochim. Biophys. Acta.112*, 168 (1966), (V. Sasisekharan and C. Ramakrishnan).

38. A proposal of standard conventions and nomenclature for the description of polypeptide conformations, *J. Mol. Biol. 15*, 399 (1966); *Biopolymers 4*, 121 (1966); *J. Biol. Chem. 241*, 1004 (1966) (J.T. Edsall and others).

39. The conformation of arginine side group and its variations, *J. Mol. Biol. 15*, 232 (1966), (S.K. Majumdar and others).

40. The stability of two-bonded collagen helix, *Biochim. Biophys. Acta 120*, 457 (1966), (C.M. Venkatachalam).

41. Stereochemical criteria of polypeptide and protein chain conformation III Helical and hydrogen-bonded peptide chains, *Biophys. J. 6*, 849 (1966), (C.M. Venkatachalam and S. Krimm).

42. Conformation of side groups in amino acids and peptides, *Biopolymers 4*, 495 (1966) (A.V. Lakshminarayanan).

43. Polypeptide chain conformation, *Fed. Proc. 25*, 346 (1966).

44. Stereochemistry of nucleic acids and polynucleotides I Theoretical determination of the allowed conformations of the monomer unit, "Conformations of Biopolymers" Vol. 2. Edited by G.N. Ramachandran and published by Academic Press (1967), page 641, (V. Sasisekharan and A.V. Lakshminarayanan).

45. Conformational Studies of Amylose, "Conformations of Biopolymers" Vol. 2. Edited by G.N. Ramachandran and published by Academic Press (1967), page 721, (V.S.R. Rao and others).

46. A study of the conformation of amino acids, "Conformations of Biopolymers" Vol. 2. Edited by G.N. Ramachandran and published by Academic Press (1967), page 61, (A.V. Lakshminarayanan and V. Sasisekharan).

47. Stereochemistry of polypeptide chains - comparison of different potential functions. "Conformations of Biopolymers" Vol. 2. Edited by G.N. Ramachandran and published by Academic Press (1967), page 83, (C.M. Venkatachalam).

48. Structure of polyglycine II with direct and inverted chains, "Conformations of Biopolymers", Vol. 2. Edited by G.N. Ramachandran and published by Academic Press (1967), page 429, (C. Ramakrishnan and C.M. Venkatachalam).

49. Absolute configuration of glucosamine, *Biochim. Biophys. Acta 148*, 317 (1967), (R. Chandrasekharan and K.S. Chandrasekharan).

50. Hydrogen bonding and conformation of polypeptides, "Fibrous Proteins" Edited by W.G. Crewther and published by Butterworths, Australia (1967), page 71, (C. Ramakrishnan).

51. Molecular architecture of collagen, *J. American Leather Chem. Assn. 63*, 160 (1968).

52. Analysis of permissible conformation of biopolymers, "Structural Chemistry and Molecular Biology", Edited by A. Rich and N. Davidson and published by Freeman & Co USA, page 77 (1968).

53. Possible formation of left handed alpha helix for poly-L-serine, *Biopolymers 6*, 461 (1968) (K.P. Sarathy).

54. Stereochemical criteria of polypeptides and proteins IV Standard dimension for the cis peptide unit and the conformation of cis polypeptides, *Biopolymers 6*, 1255 (1968), (C.M. Venkatachalam).

55. Inter-chain hydrogen bonds via bound water molecules in collagen triple helix, *Biopolymers 6*, 1649 (1968), (R. Chandrasekharan).

56. Conformation of polypeptides and proteins, *Advances in Protein Chemistry 23*, 283 (1968), (V. Sassisekharan).

57. Molecular forces in physics and biology, *Proceedings of the DAE Symposium on Nuclear Physics and Solid State Physics*, IIT Madras (1968), page 161.

58. Need for non planar peptide units in polypeptide chains, *Biopolymers 6*, 1494 (1968).

59. Single chain triple helical structure, *Biopolymers 6*, 1771 (1968), (B.B. Doyle and E.R. Blout).

60. Stereochemistry of biopolymer conformation, *Nobel Symposium 11 (1968) - Symmetry and Function of Biological Systems at Macromolecular Level*, Edited by A. Engstrom and B.S. Strandberg and published by John Wiley New York (1969), page 79.
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65. Boolean Vector Matrix formulation of logic. (Lectures L1, L2, L3). March 1987 (78).

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74. On-going studies on MATLOG. Reexamination of the subprogram LGRAPH. Dec. 1988 (Ravi Upadhyaya) (54).

75. On-going studies on RAGA Theory of solution of crystal structures purely from intensity data with examples of 2D structures belonging to space group P1,. March 1989 (145).

76. Common origin of all paradoxes and incompleteness in logic - Introduction of the BA-3 indefinite state B in the BMVFof the logic for the truth value of a statement which is neither provable to be true nor to be false, Aug. 1990, (61).

APPENDIX 5

Reprint of the paper from BIOMOLECULAR STEREODYNAMICS, Vol. I, Pages 1 to 36, Edited by Ramaswamy H. Sarma, Published by Adenine Press.

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Biomolecular Conformation Retrospects and Prospects (A Philosophical Review)

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Dedicated to Professor John T. Edsall

Introduction

As stated in the title, this essay is historical and philosophical–in that an attempt is made to explore the special events which led to the discipline of conformational analysis being established, and to give a bird's eye view of the development of molecular biophysics, particularly during the last three decades. Towards the end, I give suggestions as to the lines of approach for further studies that will be particularly rewarding in the future, both from the point of view of their basic importance, and their relevance to the growth of biological sciences.

Necessarily, this article is based on my personal experiences during the last thirty years and therefore many investigations undertaken by me and my colleagues are picked out for illustrating the main argument. I should emphasize, however, that full references to some extremely important papers from other laboratories are not given only because *this review is not intended to be exhaustive*, but to picture some salient steps in the development of the discipline, so that examples which are particularly familiar to me have been employed. Also, the paper is written in a conversational style, as in a delivered lecture, although I will not be talking personally in the conversation.

In his letter asking me to contribute an introductory paper for this Conversation, Dr. Ramaswamy Sarma has mentioned how he was "a child playing in the coconut groves of Kerala" at the time when Molecular Biology was born in the late 40's and the early 50's. Although I am also a son of the same soil of Kerala, I had the good fortune of being a fully developed scientist at that time, but one who was waiting on the threshold before deciding whether to enter this new stream or not. In the late 1940's, after taking a doctorate degree working with Prof. Sir C. C. Raman, I went to Cambridge, England and learnt at first hand the latest developments in crystallography. I had the good fortune to meet there Perutz and Kendrew who were at that time considered to have taken up an insurmountable task, namely that of solving the structures of compounds whose molecular weights were in the region of many thousands, while solving the crystal structures of even a molecule with 20 atoms was considered an achievement. A couple of years after I returned to India, I was lucky to be made the head of a new department in Madras, mostly devoted to research and having very little of teaching. Further, the laboratory was new and I could develop my inclinations in any direction that I wanted, subject to its being within the broad discipline of physics as it was understood then. I desired to start research on biomolecular structures as studied by methods of X-ray crystallography, the latter of which was familiar to me both from my earlier experiences with Raman and later in Cambridge.

I should perhaps explain why I was attracted to this fascinating subject. This is not merely a personal history, but it has relevance to the reason why researchers in the field of biomolecules turned in the way they did from about the beginning of the 50's. Even in the first year of my pre-doctoral studies in the early 40's with Raman, I was attracted by two books on his shelf, namely, "Nature of the Chemical Bond" by Linus Pauling, and "Natural and Synthetic High Polymers" by Kurt Meyer. These left a profound impression on me, although at that time I was working mostly on optics and diffraction theory under Prof. Raman. I took crystal chemistry as an extra-curricular subject of study and as part of this, crystal structures came in for serious consideration. Even at that time, I used to wonder why so few of the materials that formed the building blocks of living systems were fully explored by crystallographic techniques. No doubt, the structures of silk and of cellulose and related materials were reasonably well established, by studies starting right from the 1920's, and finally confirmed by the work of Meyer and his coworkers. Similarly the pioneering studies made by Astbury on keratin, myosin, etc., had clarified the fact that there exist two types of structures in the fibrous proteins, namely of the α and β types.

Alpha Helix–The Progenitor of Molecular Biophysics

I now come to the key event that took place in the field of biomolecular structure, namely the publication of the beautiful series of papers by Pauling and Corey (1) which appeared in the *Proceedings of the National Academy of Sciences of U.S.* in 1951. I read every one of them in our library (perhaps I was the only person in Bangalore who read them all), and I was thrilled by the revelation of so much of order existing in the materials of the living world. Leaving personal feelings aside, looking back from today, nobody will contradict me if I say that the enunciation of the α-helix by Pauling based on the planar peptide unit, and the crucial importance of the formation of strong and straight NH ... O hydrogen bonds, which he demonstrated, were the starting point for almost all that has taken place since then in the solution of the structures of various biopolymers. Perhaps, as a crystallographer, I should mention a certain aspect about Pauling's α-helix, which those who are not crystallographers would not have appreciated so clearly. There is a "dogma" in crystallography, according to which screw symmetry can have only axes of orders 2, 3, 4 and 6. Both 5 and the higher integers, as well as non-integral values for the number (n), of units per turn, are disallowed for crystal structures. I use the word dogma, because unfortunately, it has led to a delay in the realization of the true nature of the helical symmetry in many biopolymers. It needed the clear sight and wisdom of a person of the magnitude of Pauling to realize that what is important for the stabilization of the structure of a biopolymer chain, is not crystallographic considerations, but crystal-chemical principles. In solving the crystal structures of a large number of compounds, he always had chemistry and chemical-physical considerations in the forefront in understanding the principles regarding the nature of the three-dimensional architecture of molecules, rather than the more mundane aspects like symmetry, number of molecules per unit cell etc. Therefore, when he found that the α-helix had a non-integral number of units per turn, he had no hesitation in putting it forward as a possible structure for the polypeptide chain. I say this because, at that time when I saw Pauling's papers I was rather surprised at the fact that n was 3.6, for his α-helix, since this would not fit into a nice crystal structure with one of the classical screw axes. Even making it 18/5 was only a way of getting over the non-integral nature.

That a non-integral number of residues per turn is not at all impossible for single helices came out even more prominently one year after the α-helix appeared, namely in 1952, when Cochran, Crick and Vand published their famous paper (2) on the Fourier transform of helical structures. I am quite sure that it was this confidence in chemical principles (as enunciated by Pauling), rather that crystallographic requirements, that removed the obstacle of a multiple of six as a necessary number of units per turn in the DNA helix (3) that Watson and Crick worked out. (I have not talked to them but it would be very interesting to know what the feeling about orthodox crystallography was at the time on this matter. In fact, even such stalwarts like Bragg, Kendrew and Perutz missed discovering the α-helix, in their exhaustive study (4) published in 1950 (one year before Pauling's), because their emphasis was on configurations that were consistent with crystal symmetry.)

It is not very surprising that, following Pauling's alpha helix in 1951 and the DNA double helix in 1953, we were lucky in working out the triple-helical structure of collagen (5) in 1954. In fact, when Kartha and I worked out the structure, we were looking for a 3-fold screw symmetry for the structure–I shall say later about how the 3-fold symmetry was arrived at–but since we had not fully realized that non-essentialness of a crystallographic screw axis at that time, we did not look for a non-integral number of units per turn. Actually, the structure we proposed was based on a hexagonal unit cell, having 3-fold symmetry. However, all the essential physical and stereochemical requirements of the collagen structure were there in it-namely facts known about infrared dichroism, amino-acid composition, (such as fitting in of proline) and so on. However, within one year after this, when we got a good x-ray pattern of collagen right in our laboratory, we revised the value of n from –3.0 to –3.3, a non-integral number (6). This was actually done by analyzing the pattern using the formulae for such a non-integral helix, as given in the paper of Cochran, Crick and Vand mentioned above. By that time, biopolymer workers had attuned themselves to non-integral numbers, although an aura of the mystery of integers still lingers, so that, even now, many express non-integral number of units per turn as ratios of integers-for example, 47/13 for the α-helix of poly-L-alkanine, and 10/3 for collagen.

Soon after the enunciation of the collagen helix in 1954, even in the year 1955 itself, polypeptides related to collagen, like polyglycine II and polyproline, were found to have an exact three-fold axis. But, even more interesting was the fact that the unit height (~3.0Å), which Kartha and I had worked out for this helix from stereochemical considerations, was actually found to be true for these polypeptides. Since then, numerous α-helical structures and β-type structures have been demonstrated for synthetic polypeptides, and also quite a few polypeptides containing Gly and Pro, having the collagen-like helix have been observed. In view of the ubiquitous occurrence of this third type of structure, I would like to suggest the name γ-structure as a generic term for all polypeptide structures having a collagen-like configuration–irrespective of whether the number of units per turn is exactly three or not. The term γ-helix will signify a peptide chain configuration having a lefthanded helix close to three units per turn, and a unit height of the order of 3Å. (There is likely to be no confusion with the γ-helix that Pauling put forward in 1951, since we know from energy considerations that this is unlikely to occur and as it has also never been observed.) In terms of the (ϕ, ψ)-angles, the α-, β- and γ-structures will lie in the vicinity of (-60°, -60°), (-120°, 120°), (-60°, 120°). (See Table I).

Generation of New Ideas and Their Detailed Application

Since this essay is philosophical in tone, I would like to discuss certain aspects related to the enunciation of completely new ideas like the α-helix, which is the result of inspired thought. Although it is likely that an "inspiration" is imperative for the breakthrough to occur, it has

Table I

Dihedral Angle Values and Helical Parameters of the Possible all-*trans* Polypeptide Helices.

	Dihedral Angles			Helical Parameters		Reference
Type or Name	ϕ°	ψ°	ω°	n	h(Å)	
Alpha type – Intrachain $j \rightarrow 1$						
$2.2_7 (j = 3)$[1]	-78°	59°	—	2.2	2.7	(30)
3_{10} $(j = 4)$[2]	-49°	-26°	small	3.1	2.0	(30)
α $(j = 5)$[3-4]	-47°	-57°	~0°	3.6	1.5	(30)
π $(j = 6)$[2]	-53°	-70°	small	4.5	1.1	(30)
Beta type[3-4]*–Interchain H-bonds**						
Silk, Poly-Gly	-140°	135°	†	2.0	3.45	(30)
β-keratin	-125°	120°	†	2.0	3.35	(30)
*Gamma type–Interchain H-bonds**						
(a) Hexagonal lattice						
Poly-Gly,-Pro,-Hyp[5]	-80°	150°	†	-3.0	3.1	(7)
*(b) Triple-chain, coiled-coil structure**						
Collagen	-75°	160°	†	-3.3	2.9	(7)
Delta-type–Intrachain H-bonds $1 \rightarrow j$*						
δ (j = 4)[6]	-100°	-80°	~-10°	-4.2	1.25	(8)

*Dihedral angles rounded off to 5°.

†A range of ω is possible for these.

[1] This helix has not been observed, although the nucleus of it has been observed for a pair of peptide units.

[2] This occurs occasionally in globular proteins.

[3] Common in globular units.

[4] Widely prevalent for polypeptide chains and in fibrous proteins.

[5] Occurs also for mixed polypeptides of these, especially having the sequence $(\text{Gly-X-Y})_n$, with X or Y as Pro or Hyp.

[6] Poly-L-diamino-propionic acid, poly-β-benzyl-L-asparate and related polypeptides, probably have this helical structure.

also to depend, to a large extent, upon previously existing observational data and theoretical ideas. Also, it is quite likely that, although the essential principles of the new idea are absolutely correct and indisputable, the intimate details and nuances that are worked out regarding this need not necessarily be all correct. I shall illustrate this by a re-examination of what happened in the 1950's. This period is sufficiently far off for us to revisit, and I am doing this here with the purpose of pointing out that, when new theories are put forward, we should not criticize them too much, just because some consequences of the theory are obviously incorrect. In spite of this, the positive aspect must be given credit, even though there may be negative consequences. The latter could often be remedied by making suitable improvements or modifications in the theory.

This is seen very well by a re-examination of the 1951 series of papers by Pauling. Even in his first paper, he mentions about a helix which he designates as the γ-helix, at the time as he discusses the α-helix. However, we now know that the γ-helix has not persisted, even though the α-helix has revolutionized molecular biophysics. This does not mean that the theoretical formulation which gave rise to the γ-helix is wrong. It only means that there were still some factors which were not completely included in the approach that led to the γ-helix. I will have more to say about this later, when I deal with the criteria that could discriminate between a good biomolecular structure and a bad one. In fact, the α-helix coordinates as given by Pauling in 1951, would not be acceptable today, because they do not satisfy the contact criteria that we now adopt. One finds the same thing about the early coordinate data of the DNA helix that was worked out by Wilkins. The same thing is true of the first coordinates of the correct non-integral helix of collagen (5) which Kartha and I worked out and which was criticized, on this point, by Rich and Crick. However, all these three structures are essentially correct, as is shown by the fact that, when better data and better mathematical techniques were available, they could be used to refine all these structures to ones which are perfectly good from the point of view of their packing energy. The point I wish to make here is that, in retrospect, if the structures of the α-helix, the DNA helix, and the collagen helix, as they were put forward in the 1950's, were examined from the 1980 criteria, the actual structures proposed would be declared to be unacceptable. But with the knowledge and facilities available in 1980, they could be refined to acceptable structures, perhaps in 5 minutes of computer time.

Purely out of curiosity, I examined the literature from 1950-55 about the types of helices that had been predicted and those that have survived. I am not giving an exhaustive list, but only a few examples to show how infantile the stereochemist's approach to model-building was in those days. Thus, Pauling gave a structure for collagen in his 1951 series which was believed to fit several features of x-ray diffraction, infrared spectroscopy, and so on, and yet was nowhere near the correct structure. It even contained *cis* residues, which were shown not to exist by infrared studies, later in 1954. Again Crick (probably influenced by the double helical nature of DNA) proposed *a double helix for collagen* in 1954 and showed by an optical diffractometer study that it fits the x-ray diffraction pattern for collagen. This again contained a *cis* peptide unit not present in collagen and the only feature in which it agrees with the finally determined structure is that the NH...O hydrogen bonds are nearly at right angles to the helical axis, as given by the infrared dichroism studies. During that time (1950-54) several other wrong structures for collagen were given which I do not wish to quote here, but may be seen from my article in the "Treatise of Collagen" Vol. 1 (7).

Coming to feather keratin, Pauling, influenced again by the success of his α-helix for α-keratin, proposed that feather keratin consists of α-helices. Here also, we in Madras were influenced by the collagen helix, and proposed that feather keratin contains a collagen-like structure for its helical chain. We were encouraged in this, to a large extent, by measurements on the optical rotation $[\alpha]_D$ of soluble feather keratin, which give a value of –400°, as compared with –350° for collagen, –100° for the β-structure and +100° for the α-helix. However, both of these have been shown to be wrong by later studies made by Fraser who prefers a β-structure, although it is given a super-helical left-handed twist, which will bring it close to the collagen orientation on the average.

Since we are talking of helices, I might add a few lines about the different types that have been observed so far for polypeptides. We have already considered three well-known ones–namely, α-helix occurring in α-keratin and myosin, the β-helix which occurs in β-keratin and silk, and the γ-helix which occurs in collagen and polypeptides related to it. The question arises whether there are any more standard helices for the **L**-polypeptide chain. In fact, no new types were discovered since 1954-55, until three or four years ago, when a left-handed helix, somewhat similar to the α-helix in being single-stranded and having intrachain hydrogen bonds, was proposed (8), and named as the δ-helix. This is, however, different from the left-handed α-helix, in that it has hydrogen bonds in the opposite direction to that in the α-helix helices. It has interesting possibilities, and its (ϕ,ψ)-values are also given in Table I. However, we may mention that the long delay in its formulation was due, to a large extent, to the reluctance to question some well-accepted ideas, like the rigid planarity of the peptide unit, which hindered the search for such new possibilities. Some special experimental and theoretical stimuli were needed for it to be discovered.

Its establishment as a possible stable structure for **L**-polypeptides came only after the existence of non-planarity in peptide units was established, and the energy associated with this type of distortions had been calculated from quantum chemistry. Experimental evidence that some features of it were detectable by NMR for a small sequence in the lac repressor also played an important part in its postulation (8). Very recently, Bansal and coworkers (9) have proved by energy minimization that the so-called ω-helix, with $n = -4$, supposed to occur for poly-β-benzyl-L-aspartate, is really the δ-helix with $n = -4$, since the latter is lower in energy than the former by about 10kcal/mole per residue.

Different Approaches in Scientific Research, as Shown by Examples in Biopolymer Conformation

Since this article deals with some general aspects of scientific research with special reference to biopolymer structures, I shall now consider different ways in which such a study may be undertaken, and I shall illustrate them with experiences in our own laboratory. In particular, I shall summarize the collagen structure story in which luck played a great part, and the (ϕ, ψ)-plot discovery, which was completely preplanned and was the culmination of a programmed approach.

Leap in the Dark. As I told you, our interest in collagen arose from an attempt to follow up some of the problems arising from the studies that Pauling and Corey had initiated; but I did not know where to start or how to go about getting a biological fibre specimen. It was a curious coincidence that both these difficulties were simultaneously resolved for us as a result of the visit of Professor Bernal to the Madras University some time in 1952, or 1953, soon after I had joined there. He told me (confidentially, of course) that he did not believe that the Pauling-Corey structure for collagen was correct and indicated that the problem was wide open. He even went one step further, and told me that, right in the Biochemistry Department of Madras University, which was only one floor above ours, they had a sample of collagen–actually it was elastoidin (shark fin ray collagen)–whose amino-acid composition had been determined by Prof. Damodaran and colleagues of that department.

As soon as Bernal left, I contacted Biochemistry and got this material. It was my first experience of mounting a biological fibre on an x-ray camera and taking its fibre diagram. The picture showed, in principle, all that had been stated in the literature for collagen; but it was too diffuse. I did not know at that time that this material really consisted of two parts (which has been found out only during the last ten years or so), one of which is truly collagen-like, while the other is some other protein rich in tyrosine. However, I could see that this fibre pattern was not good enough for our studies, and we therefore looked up, in great detail, the literature connected with x-ray diffraction pattern of collagen. We then learnt that the beast patterns had been obtained using kangaroo tail tendon. But where to go for a kangaroo tail in India? A solution to this also became possible very quickly, because only a few months earlier, the Central Leather Research Institute had been established in Madras and, as luck would have it, this was also next door to our University campus. I need not tell you that the protein in leather is almost completely collagen. Therefore, I went to the Deputy Director of that Institute, Dr. Y. Nayudamma, and asked him whether he could give me a good fibre of collagen suitable for x-ray studies, and *in passing*, I told him "Kangaroo tail tendon will do very well." I then forgot about it; but imagine my surprise when only six weeks later, I received a tube containing just this material. Apparently, Dr. Nayudamma had contacts with leather technologists in Australia, and through them, he had obtained this material.

The very next day we took the diffraction pattern of this in our fibre camera and we were delighted when we found that this was as good as any reported photograph of the x-ray pattern of collagen. But it was more that that, *because this was our own photograph*, and we could measure it on whatever way we wanted. In fact, we took photographs mounting the fibre at various angles to the x-ray beam, and careful measurements made on these provided very useful data for evolving the finer details of the structure of collagen.

Perhaps one more contributing factor to the success of my studies on collagen should be mentioned, and that is the fact that Gopinath Kartha, who had obtained his Ph.D. from Bangalore working with me, had come over to Madras to continue his post-doctoral studies. He was a trained crystallographer and this greatly helped in making this investigation. On the other hand, the laboratory in Madras was new and we had practically no crystal models, or material for making such models. In building a structure, therefore, we had to use the ribs of coconut leaves which were used for linking peptide units, which were drawn on cardboard, joined with one another using soft wax at the Cα-atoms. The structure so obtained was very crude; but even so, the possibility of three-dimensional visualization was very useful, although this approach was supplemented by planar drawings of projections, and by calculations. Of course, we had several suggestive ideas from the literature. The essence of the planar peptide unit, as enunciated by Pauling, was at the core of it, and following it was the fact that only *trans* peptide units can occur in this structure, as indicated by infrared data published about that time (1954) by Astbury, by Pauling, and by Crick, in their earlier attempts at building the collagen structure. This was a very happy choice, because, as you all know, *cis* peptides do occasionally occur in proteins and, even now in 1981, we do not know why–I shall explain this later in relation to a recent study of ours.

The occurrence of glycine as one-third of the total number of residues is the most conspicuous and universal feature of collagen from all sources. We took that as the foundation for our structure, namely *that glycine must occur at a position in the helix where no other side group* (not even CH_3 as in alanine) *can exist*. We took the clue from Pauling that glycine occurs at every third position, which very naturally explains the 1/3 frequency of this amino acid. (There was no clear-cut evidence either for, or against, this assumption at that time.) As infrared data indicated, the NH and CO bonds are nearly at right angles to the fibre axis. With these in our mind and also employing a crude interpretation of the x-ray pattern, that it had a left-handed 3-fold screw with approximately 3Å as the repeating unit, we worked out the first structure. The left-handedness arises because the rigid ring of proline and hydroxyproline (specific to collagen), without any modification of the stereochemistry demanded by other considerations.

This was published in *Nature* in 1954 by Kartha and me (5). By this time a young student, Ambadi, who is an excellent experimenter had taken inclined-beam x-ray photographs of a collagen and when we analyzed this according to the formula of Cochran, Crick and Vandt it led us unmistakably to the non-integral number 3.3, or something very close to it, as the number of units per turn. We therefore re-examined the 1954 structure. The presence of proline, with the rigid side-chain-backbone interaction, demanded that the modified structure can have only one pattern–namely a left-handed minor helix, with a right-handed super-helical twist of about 30° (~0.3/3.3 = 1/11 of a full turn of 360°.) The details of this and the method of understanding the collagen structure are given in my two articles (a) in Treatise on Collagen, Vol. I (7), and (b) Biochemistry of Collagen, 1976 (10). So I shall not say more about this, since we are not discussing collagen as such, but with the approaches that helped us in this study. However, the architectural scheme of the backbone in collagen is shown in Figure 1.

Ignorance is Bliss. If I may say so, a certain naivete on our part helped us in getting the solution, because we did not know enough about the literature in the protein field to be influenced by any other considerations. For instance, by that time, Gustavson had shown that hydroxyproline is very important for collagen and that it leads to greater thermal stability to the collagen fibre. Also, an early study by Stetten (11) had indicated that *only proline is incorporated* in collagen and *hydroxyproline is not incorporated*, so that hydroxylation should take place after incorporation of proline. If we had known all these, we would have run after the presence of hydroxyproline as one of the essential features of the collagen molecular structure, (which it certainly is from the chemical point of view, and even from the physical point of view, as we ourselves proved in the early 1970's). However, the work we did in 1972-73 could never have been done in the 50's for absence of other vital information, and it would have been a wild goose chase. Thus, as the saying goes, "Ignorance is bliss!" As a matter of fact, none of the other workers investigating collagen at that time also gave a moment's thought to hydroxyproline, although they all, like us, found the right modification of the triple helix which will incorporate proline and which will fit the x-ray pattern, namely to make $n \simeq -3.3$, or $-10/3$, for the individual minor helices.

Pre-planned Attack. I shall compare the way in which the collagen work was done, namely by taking a leap into the dark, with a thoroughly planned investigation of ours, leading to the enunciation of the (ϕ, ψ)-plot, which came as a result of years of concerted effort. It is a long story. Sometime after '55, collagen had become a finished product. Kartha left for Europe and U.S.A. and it was not very profitable to refine the structure, since the x-ray pattern did not have too much of information for this purpose. We therefore turned into biomolecular crystallography and studied the crystal structures of a number of amino acids.

In working out the structures of these amino acids, we had to study the available literature on amino acid and peptide crystal structures. Also Sasisekharan, who had joined me for his doctoral work, did a thorough refinement of the collagen structure, purely from theory, namely the point of view of getting a "good" structure free of "bad contacts." The attempt was empirical, and we used the information we could gather about various amino acid conformations from the available literature. Again, I should mention that no models were used in this; it was all drawings and calculations. In fact, every structure we studied was looked at, only as a projection drawn on paper. In this way, we got thoroughly experienced in changing angles between bonds by one degree, or less, and changing the distances between atoms by one-tenth of an Å. However, in building such structures, we always met a stumbling block and that was that we did not know how to access whether a structure was good or not good–that is to say we had no quantitative criteria for checking whether a theoretically proposed structure of a biomolecule, or biopolymer was acceptable or not.

This led us to an analysis of available crystal structures on peptides and amino acids. Not surprisingly, most of these were from Pauling's own laboratory at Caltech but the data had not been analyzed in the way that we did–namely to find out what were the ranges of the variation of different parameters,

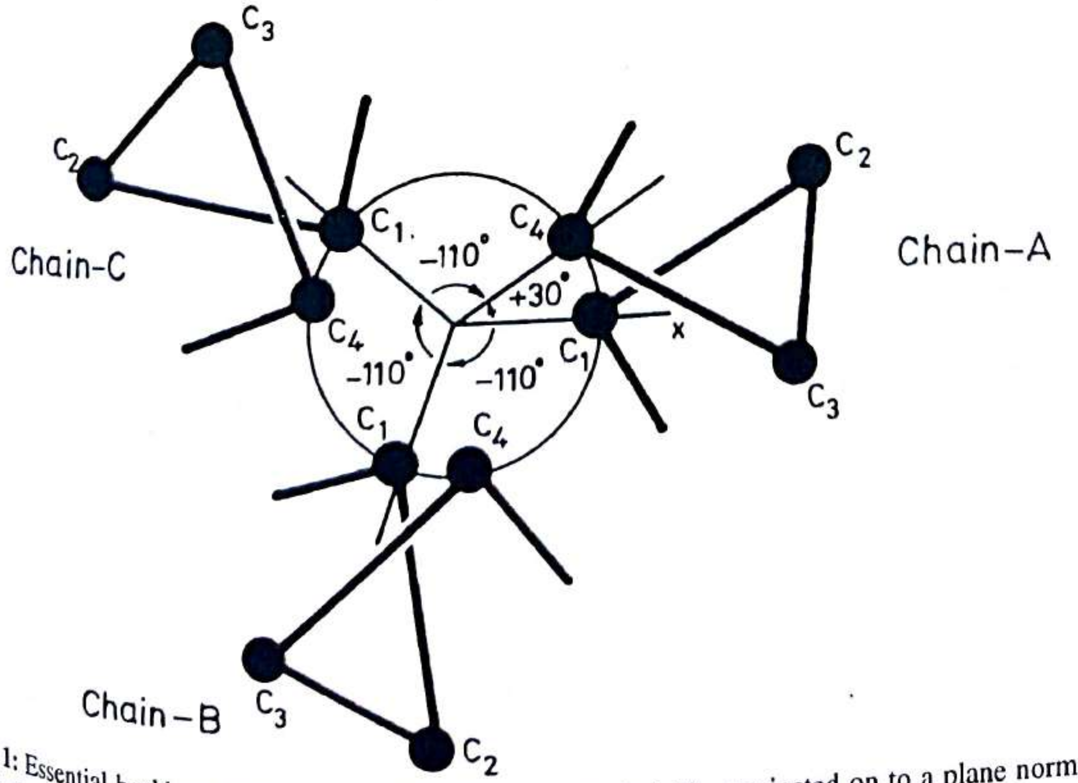

Figure 1: Essential backbone architecture of the collagen triple helix, projected on to a plane normal to the helical axis.

such as bond length, bond angles, and so on. The values of covalent bond lengths and bond angles were pretty well known. But what are the limiting distances for van der Waals contacts were completely unknown at that time. In fact, the literature on crystal structures never listed all the non-bonded contacts except what the author "felt" was a short contact, and we had to calculate these for various structures that were available.

We did this, although we had only desk calculators for this purpose. About that time, another young man, Ramakrishnan, had also joined for his doctorate, and Sasisekharan had practically completed his doctoral work, so that I had a young person to whom the crude labor could be given, and another who could help in the refined analysis of the data. Very soon, in the early 1960's, we discovered certain irregularities in the limiting contacts. But the main question still remained, as to how exactly systematic variations could be made in building up the structure of a molecule, that bond angles could not be changed very well, and luckily, we did not press in this direction, because it would have been a fruitless task.

However, during Sasisekharan's approach to the refinement of the collagen structure, we had adopted a technique which involved rotations about certain lines. In this case, it was the "virtual bond" C_1^α $-C_2^\alpha$ in a peptide unit with a rigid planar structure. What we did was to rotate the peptide unit about this line over a range of angles that permitted the interbond angles at the C^α-atom to remain within the allowed range of 110° ±3°. While this was a reasonable solution, it was extremely cumbersome and we wanted to improve on this. It was this long search for a satisfactory and convenient way of building a peptide structure that led finally to the very simple idea that these rotations could be taken to occur about the covalent bonds themselves which join each C^α-atom with the next atom in the chain, namely the two bonds C^α–C′ and N–C^α, as shown in Figure 2.

The evolution of this idea took a couple of years. In the beginning, we found out only the effects of the restriction of the backbone atom-atom non-bonded distances and this was published in the volume reporting the symposium on Collagen (12) held at the Leather Research Institute in 1961. Very soon, this was extended to the effect of side-chain-backbone contacts also–with only the CH_3 group of alanine being included for the side chain. The work was back-breaking, and it took almost 6 months for Ramakrishnan to obtain the complete data, once the procedure was quite clear. But, when the data were plotted in what we now call as the (ϕ, ψ)-map, the results were really rewarding. We could see at once that every structure that had been determined at that time had its o- and ν- values within the ranges that we had marked in this map using the contact criteria. This was published in 1963 in the *Journal of Molecular Biology*. (13)

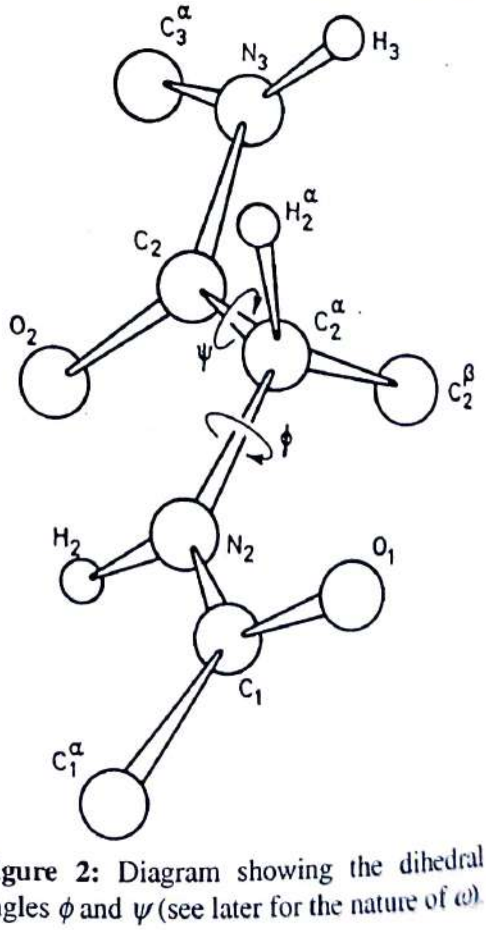

Figure 2: Diagram showing the dihedral angles ϕ and ψ (see later for the nature of ω).

I have often been asked as to how confident we

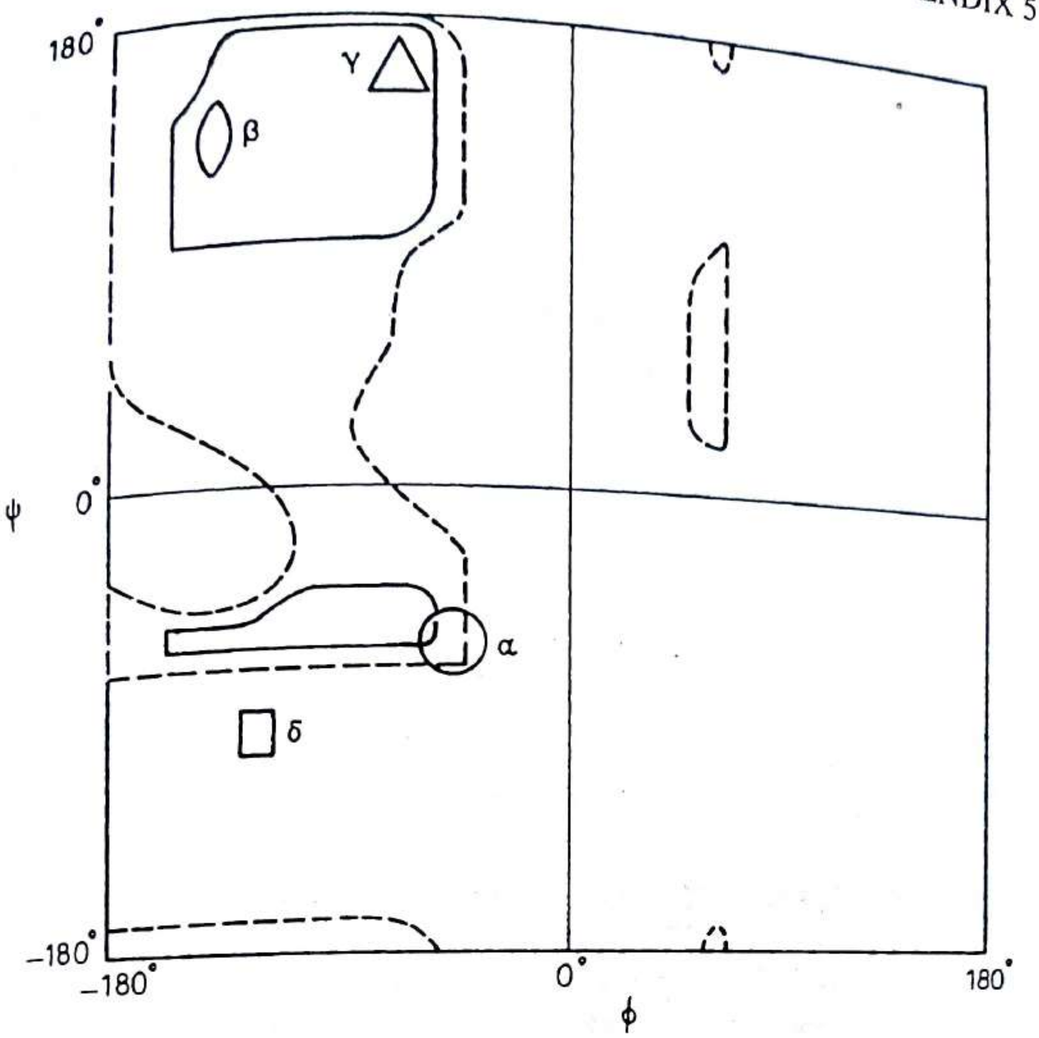

Figure 3: The (ϕ, ψ)-plot, according to the IUPAC-IUB conventions.

were about the contact criteria. As shown in Figure 3, two sets of contacts were given–namely the "normal limits," and what we call "extreme limits." This was necessary, because when we examined the observed crystal structures, we found that most of the non-bonded contacts were above the normal limits, but in some rare examples, these were violated appreciably. The choice as to where the limit of the normal contacts came, and where the limit of the extreme contacts should be put, was empirical, based purely on our judgement. But, it is really gratifying to note that, even now, more than 15 years after the formulation was made, the contact distances which we had indicated have remained practically unchanged, and the map drawn in '62-'63 is still valid. The one and only improvement, perhaps, is the recognition, in recent years, that the C...H and H...H contacts could be softened a little more, by reducing their limiting values by 0.1Å. I shall say something more about this softening, at a later stage.

What I wish to emphasize is that, very often, a result of importance like the present one occurs only as a result of a long and painstaking search. In our case, we did not know what the result of the search would be; but we wanted some rule that we could use, whereby we could say when a structure is good and acceptable and when it is not. In fact, I was very pleased when Prof. Pauling, in his discussion with us when he came to Madras in 1967, said that, in Caltech, they had studied more amino acid and peptide structures before 1960 than in any other laboratory, and rightfully the (ϕ, ψ)-map should have been discovered in Caltech.

Strategy of Waiting for the Right Time to Come. Now, I shall illustrate a type of research in which one has to wait a long period for the right type of information to become available, so as to complete the line of approach that was adopted. It was particularly so in connection with the consummation in the 1970's of the structure of collagen, postulated from theory as early as '54-'55.

One of the difficult questions in the intervening period up to about 1965 was this. It appeared that the best structure that is possible for the backbone (as worked out from conformational theory) is one in which there is only one strong hydrogen bond of the type NH...OC, while experimental data indicated that there are two of them, for every three residues. In fact, in the early structure which we proposed there were two. But, calculations of energy indicated that, although it had an extra hydrogen bond, the short contacts introduced thereby destabilize the structure, and the two-bonded structure was probably not superior to the single-hydrogen-bonded structure. In fact, there was no way of reconciling the sharp difference between the theoretical deduction of a structure with a single hydrogen bond as being the best, and the experimental observations that two hydrogen-bonded backbone NH groups could be detected for every three residues. (The third NH bond points in a direction away from the center of the triple helix and can never form an internal backbone-backbone hydrogen bond.) I remember many occasions during conferences, at which my views were asked about this, and I used to say that one should somehow find a *via media* structure between those demanded by theory and by experiment.

Actually, the answer came, in just that way in 1968, from a study which I made with Chandrasekaran in Chicago, on the binding of water to the backbone of the collagen structure (14). Incidentally, the fact, that such a hydrogen bond between the second NH and a carbonyl oxygen via water might exist, had been stated by us in a paper published as early as 1956, but we had completely forgotten about it after that. When the subject was re-examined in 1968, Chandrasekaran had absolutely no difficulty in fitting the water molecule at a location satisfying the requirements mentioned above. In fact, I was really wonderstruck at finding that the best single-hydrogen-bonded structure that Sasisekharan had worked out, about 6 or 7 years earlier, was just right and could accommodate this extra water molecule with practically no change in the positions of any of the atoms already included. All that we had to do in Chicago was to fit in the water oxygen O_W, such that the hydrogen bonds NH...O_W and O_WH_W...OC were both good and strong. Incidentally, we found that one more water molecule per tripeptide could be fitted between the carbonyls, but the H-bonds were not too strong. These data were in agreement with various types of information that had been gathered about the binding of water and the formation of hydrogen bonds in the collagen structure by experimental techniques. Some of them, like the one on the presence of two NH...O bonds, were available a few years earlier, but not published, and some obtained about the same time, or a little later. However, it was the existence of the discrepancy between facts and theory that triggered our study in 1977-78.

But this was not the last word. Actually, when Chandrasekaran fitted the water molecules, I asked him the question "Would the oxygen of the same water *receive a hydrogen bond from hydroxyproline* if it were there?" I should mention that by that time, the importance of hydroxyproline for collagen fibril formation had been fairly well established. Unfortunately, Chandrasekaran made a mistake in locating the OH group in the 4-position of the proline ring. There are two hydroxyprolines, having the OH group in the 4-*cis* and 4-*trans* configurations, the latter of which is the correct amino acid that occurs in collagen. By a strange mistake, he put it in the wrong way in copying the data, from the published crystallographic structure of hydroxyproline on to collagen model, and he told me that the oxygen is pointed completely in a wrong direction and can come nowhere near the water OW. I felt this was very unfortunate, because I was pretty sure that we had killed two birds at one shot, namely the explanation of the occurrence of two hydrogen bonds for the backbone NH's without any short contacts, and the formation, at the same time, of an extra stable bond *via* hydroxyproline.

As with the earlier hydrogen bond *via* water proposed in '55-'56, once again I completely forgot about hydroxyproline, and we did not work on collagen until 1973 when I returned from another visit for a year to Chicago and took up my assignment in the newly formed Molecular Biophysics Unit at Bangalore. It was again a lucky coincidence that a collagen biochemist, who had worked on the hydroxylation of proline (Dr. Bhatnagar of San Francisco), should visit Bangalore just at that time, on his sabbatical leave. I told him that hydroxyproline was mysterious, and that it was not doing what it was expected to do, and I had no answer to his query. But his question stimulated me to think further about this aspect. Luckily, we had some young students who were interested in making energy calculations for biomolecules, and I gave this problem to one of them. (At that time, I had no memory that I had already given it to Chandrasekaran and that he had drawn a blank), Imagine my surprise, therefore, when within one or two weeks, this student (now Dr. Manju Bansal) came back and said that the hydroxyproline makes an excellent hydrogen bond with the water O_W, placed in exactly the same location which Chandrasekaran had given for it without taking hydroxyproline into account. Immediately, we wrote a paper for *Biophysica Biochemica Acta* (15) saying that the role of hydroxyproline in collagen is to add extra stability to the collagen triple helix, by forming an extra hydrogen bond to the network of hydrogen bonds that is normally present. Later, the structure was energy-minimized by Bansal, and shown to be perfectly satisfactory. The structure is shown in Figure 4, in a skeletal form including only the essential atoms involved in the hydrogen-bonding network con-

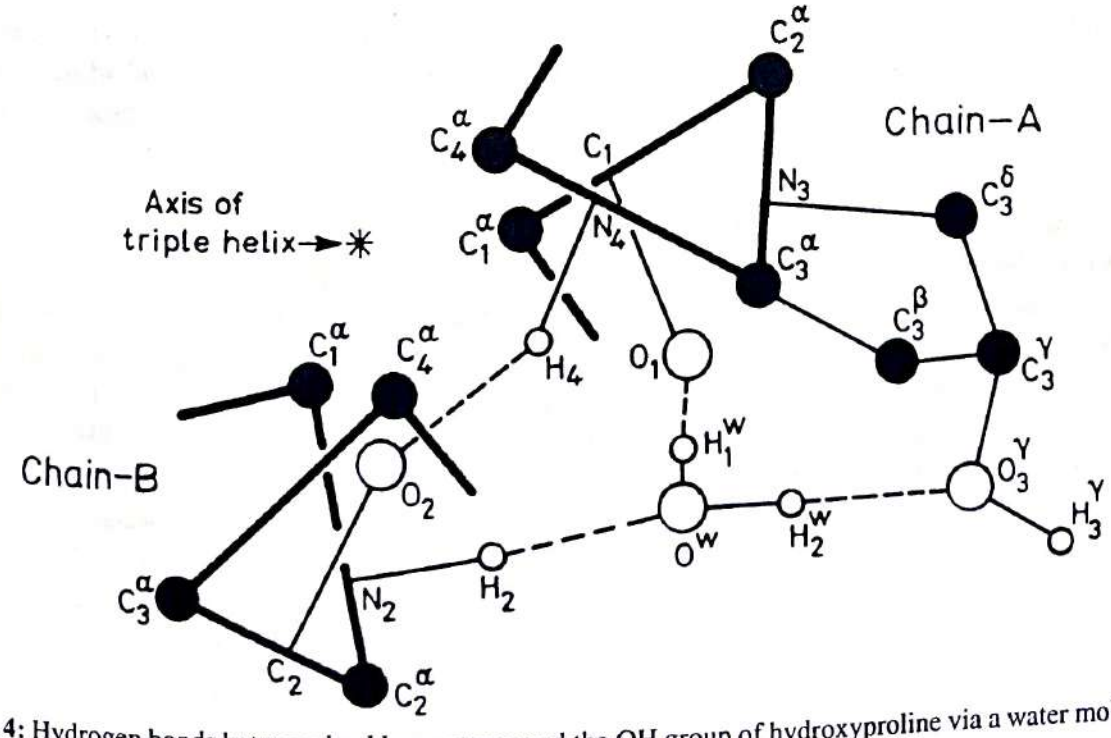

Figure 4: Hydrogen bonds between backbone atoms and the OH group of hydroxyproline via a water molecule.

nected with hydroxyproline.

Unlike the case of the firmly bound water molecules, where experimental evidence practically preceded theory, in this case experiment was simultaneous with theory. In the same year 1973 when our theoretical paper on the role of hydroxyproline was published, experimental data were also published from two laboratories showing that procollagen, which did not have the prolines hydroxylated, and normal collagen, which had the proline, at position 3 in the sequence Gly-X_2-X_3, hydroxylated to form hydroxyproline, had a difference of 15°C in their melting temperatures. In fact, it turns out that if hydroxyproline were absent, collagen of bone and skin would not be stable at room temperature, and talking facetiously, I may say that you and I would not be present here for this lecture.

Need for Stimulus. In so far as collagen secondary structure is concerned, this is the maximum information that could be obtained, except that we may hope that, one day, someone will solve the crystal structure of a protein containing the γ-helix and get more accurate coordinates of the atoms in it. However, some five years later I had one more go at the hydroxyproline mystery. About 1975-76, I edited a book on "Biochemistry of Collagen" (10) in which I wrote a short article on the molecular structure of collagen. It also contained a very long article by Prockop on the hydroxylation of collagen, and this brought out the most interesting fact that a special enzyme called proline hydroxylase is necessary for this purpose and that this enzyme had as cofactor ascorbic acid, i.e., vitamin C. I must also add that, at about the same time, I had come to know that a component of the immune response system known as "complement C1q" had, as part of its amino acid residues sequence, a part which is highly collagen-like, in that there is glycine at every third position, a reasonable amount of proline, and also definitely presence of hydroxyproline residues in the third location X_3, mentioned earlier. From my knowledge of the collagen structure, I was absolutely sure that these are sufficient to demand that the particular portion of complement would have the collagen triple-helical structure. Even without knowing whether there were three chains or not, I would have voted for the presence of the triple helix, produced even by the same chain folding itself back and forth. Therefore, I was thrilled when I learnt in 1977 that Porter, in Oxford, had actually found that complement had a triple-helical structure and there are in fact six such rods in this huge biomolecule.

One again, it was interesting to know that my conjecture was proved correct; but the matter stopped there, until another exciting consequence took place a few months later. This happened in Washington, D.C., where I was a Fogarty International Scholar at the National Institutes of Health, Bethesda. Here all the scholars were housed in a beautiful house known as "Stone House" and we met one another several times every day and there was plenty of exchange of ideas. In this way, I had a long talk with Prof. Sir George Pickering, Dean of Medicine at the University of Oxford about various things, in the middle of which I made a comment saying that Pauling seemed to believe that vitamin C will help the body resist all infection and that he claimed that it provided resistance even against cancer. Sir George Pickering said, "Bosch!" This immediately evoked a strange response from me and I saw in a flash that from my knowledge about collagen, I could prove that Pauling was perfectly right. Analyzing the thought process that led to this response, I found out that it was associated with the fact that Pickering came from Oxford, and Oxford associated itself with Porter, Porter with complement, complement with collagen, and the fact that collagen and complement both contain hydroxyproline, which requires the enzyme proline hydroxylase for its formation and requires as cofactor vitamin C. So I immediately told Prof. Pickering that it was not nonsense, and that I would prove that vitamin C will improve resistance to infection. Then, I explained to him how vitamin C is essential for the hydroxylation of proline in collagen, and since complement has as its essential part the collagen triple helix which needs hydroxyproline in it for its formation, vitamin C is essential for its synthesis. Of course, it is for biologists and medical doctors to verify that giving more vitamin C would improve resistance; but my theory could definitely explain why absence of vitamin C reduces the resistance to disease.

I was so pleased with this that I took the opportunity of writing a short paper on this, which I contributed to a Symposium on Quantum Pharmacology, which was being held in Florida in the next few months in honor of Linus Pauling's 70th birthday. Figure 5 is the illustration that was included in this paper.

Effect of Atmosphere. I believe that this paper is one of my best contributions in the discipline of conformational analysis, and what I have elaborated so far clearly indicates that one must always be on the lookout for surprises, when it comes to the question of discovery. Discoveries, naturally, cannot be made to order, but just as statistics is applied in economics and in social relations, and it is said that if there is more wealth there is more happiness (although in individual cases it may not be so), in the same way, when there is a predominance of science and scientific discussion, there is certainly every chance that bright new ideas will come out. I do not remember exactly where this quotation came from, but I am reminded of it this way–"When Greek meets Greek, there comes the spark." So, as an application of scientific philosophy towards scientific organization, I would say there is nothing more profitable than

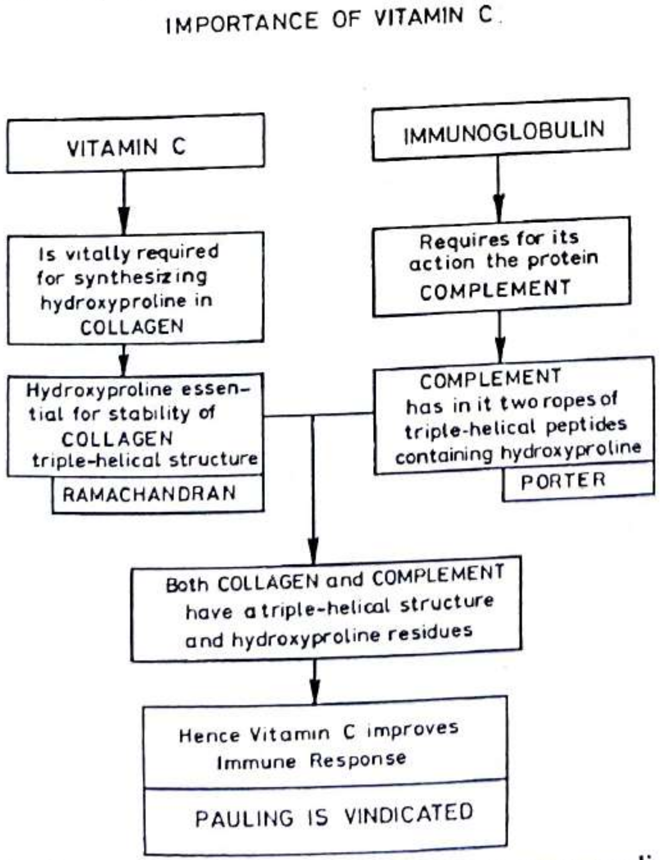
IMPORTANCE OF VITAMIN C.
VITAMIN C
IMMUNOGLOBULIN
Is vitally required for synthesizing hydroxyproline in COLLAGEN
Requires for its action the protein COMPLEMENT
Hydroxyproline essential for stability of COLLAGEN triple-helical structure
RAMACHANDRAN
COMPLEMENT has in it two ropes of triple-helical peptides containing hydroxyproline
PORTER
Both COLLAGEN and COMPLEMENT have a triple-helical structure and hydroxyproline residues
Hence Vitamin C improves Immune Response
PAULING IS VINDICATED

Figure 5: Flow chart of ideas leading to the conformation of Pauling's theory regarding vitamin C.

the type of conversation you are organizing, in which workers from different fields are meeting together to discuss a common subject, which is of importance to various branches of molecular biochemistry and biophysics.

Conformational Analysis

Now I turn to the general subject of conformational analysis in which, unlike in the case of collagen research, our studies were all directed towards a goal and specific problems were worked out which had been formulated earlier. This type of approach is as important for scientific research as the other approach–namely of walking right into an unknown forest and searching for something beautiful whose nature even you are not aware of.

Role of Conformational in Biological Activity. In this connection I am reminded of a simple illustration of what conformation is, that I give to my students. Suppose you took the human body to be a biological molecule. When this human being performs different functions, he keeps his body and arms at different angles and states of agitation. For instance, if he were swimming, his hands and legs would be rapidly going backwards and forwards. In the same way, if he is swimming in the backstroke style, his legs would make very little motion, while the hands would make a circular motion about the shoulder. If he were diving into a swimming pool, he will stretch out his hands and keep a rigid needle-like shape for his body, so that he can pierce the surface of the water with minimum resistance. On the other hand, if he is going to sleep inside a quilt, in a house without heating in winter, he will curl himself up such that his body, head, limbs, etc., assume as nearly a spherical shape as possible. (Incidentally, this is something we all do; but from physics also, this is the natural thing to do, because we reduce the surface area to a minimum and thus make heat losses as small as possible.)

What I wish to bring out by this analogy is that the shape of a molecule has very much to do with its function–in the biological systems we are interested in, and in chemical reactions in general. According to the particular type of function that it has to perform, a molecule that can assume the appropriate shape, or configuration, is selected by the living system to take that particular role.

Alpha-Glucose and Beta-Glucose Polymers. Thus, for instance, cellulose is the main building block of the bulk of the plant kingdom. It forms almost 99% of its make-up and is strong and fibrous. This is achieved because the glucose residues in cellulose take a parallel orientation and an almost straight tape-like structure. The neighboring tapes are hydrogen bonded and so are neighboring sheets of tapes, so that we have essentially a very strong fibrous material. On the other hand, the same glucose residues, but in the α-form, cannot take up this configuration. This was one of the things that was worked out in our laboratory soon after the (ϕ, ψ)-map for proteins was discovered. In 1967, V.S.R. Rao and collaborators worked out the corresponding (ϕ, ψ)-maps for cellulose and for amylose, namely for two units of β-glucose, and for two units of α-glucose (16). From the point of view of chemistry, these two differ minimally; but from the point of view of conformation, it is the difference between food and wood. The α-glucose chain forms a helical structure with plenty of space in between, so that the different helices cannot be easily joined to one another and each is in equilibrium in water, as in starch. On the other hand, cellulose is so well packed that it is insoluble in water.

Early Attempts on Other Biopolymers. Now we come back to the (ϕ, ψ)-map for proteins an polypeptides. As already mentioned, when tested against the known conformations at the joining C^{α}-atoms for the compounds that has been studied at that time, including those of the well-known α-helix, β-structure, and collagen helix, they were all found to be inside the allowed ranges of the map. This gave us enormous confidence in the criteria adopted for drawing this map-namely the limiting contact distances that were used. Therefore, we went ahead and studied as many compounds as possible that we could lay our hands upon–but restricted ourselves to those that are of relevance in biological systems. As you all know, the three types of polymers that occur in biosystems are proteins, nucleic acids, and polysaccharides. We have already discussed **L**-polypeptides that occur in proteins. In 1967, the first typical conformational data for dihedral angles related to different linkages in nucleic acid chains were worked out by Sasisekharan, along with his colleagues in our laboratory (17), and he extended this to various types of nucleic acid conformations that were known. In fact, as I shall briefly mention later, his great confidence in the power of these methods led him to postulate entirely new types of conformations for nucleic acid chains which were unknown previously, and which have been actually detected and found to be important, after their theoretical postulation.

In the case of polysaccharides, as mentioned above, the glucose polymers are simple to study. The extension of these to various other types of sugar polymers was systematically undertaken by Rao in our laboratory. Here also, after he had mastered the problems and peculiarities associated with the system, Rao diverted his attention towards still more complicated systems–namely proteoglycans and glycoproteins–in the late 1970's. These are compounds in which both peptide chains and sugar chains occur together. I can say, without any exaggeration, that these compounds have been studied theoretically best, perhaps, in our laboratory in Bangalore.

L *Imitates* D *in Penicillin*. These studies on such complex materials are not merely of theoretical interest. It so turns out that the bacterial cell wall consists of peptidoglycan and one of the most important of antibiotics, namely penicillin, acts by preventing the synthesis of a portion of the peptide chains by which different glycan chains are interlinked. It is known that the penicillin molecule is a derivative of a dipeptide **L**=Cys-**D**-Val in which, in addition a special covalent linkage occurs, leading to the formation of the β-lactam ring. Penicillin effectively prevents the combination of a peptide chain ending in **D**-Ala-**D**-Ala with the next amino acid (**L**-Lys, in most cases). The way it does this was originally thought to be by imitating an earlier segment of the peptide chain containing the same sequence of an **L**-residue followed by a **D**-residue, similar to what penicillin has. However, Rao (18) was able to show that the **L**-**D** sequence in penicillin really imitates the **D**-Ala-**D**-Ala sequence in the peptide chain, which is made possible because of the special β-lactam linkage that penicillin has. The similarity of the penicillin molecule and a stable of the **D**-Ala-**D**-Ala fragment which it stimulates, is shown in Figure 6, which has been specially prepared by Rao for this lecture. In as many as five places, the corresponding atoms in the two cases occupy the same relative three-dimensional configuration. In fact, this is perhaps the best-illustrated example of a "competitive inhibitor" of an enzyme, and I consider this as one of the most outstanding achievements of conformational theory.

In fact, this theoretical prediction of Rao has been completely confirmed, by recent studies made on another peptide which have been published in a paper which appeared in *Science* of Nov. 7, 1980 (19), and which I saw just one week before preparing this lecture. In this study, the β-turn (which will be discussed in the next section) that occurs in the lutenising hormone-releasing hor-

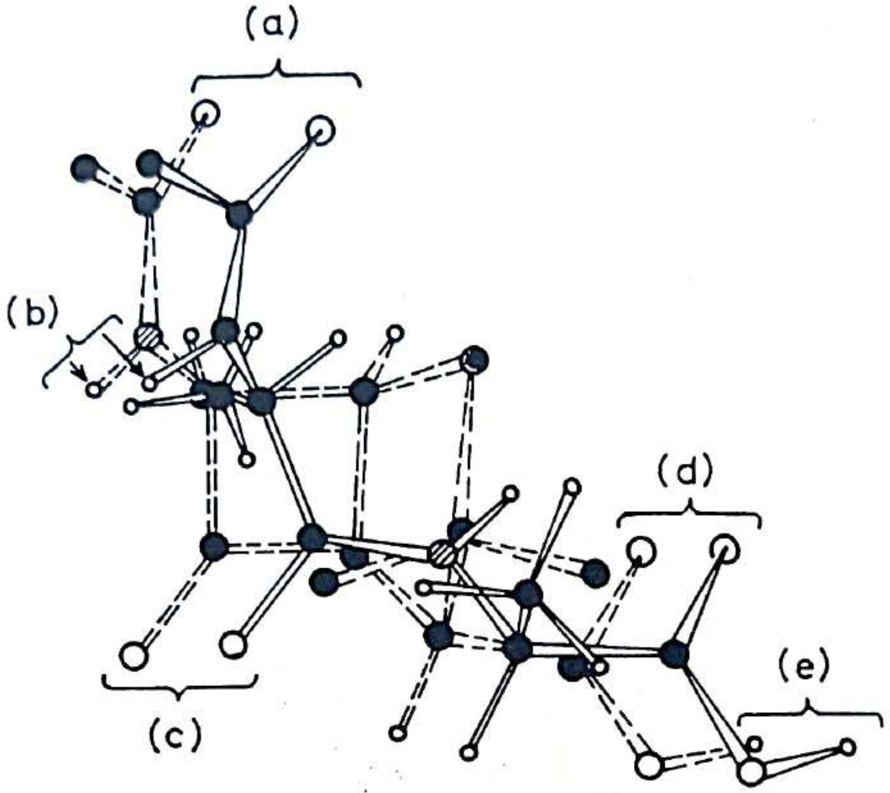

Figure 6: "**L** imitates **D**" in penicillin. The black dots represent atoms in the penicillin molecule, while the open circles stand for those in the substrate. Note the close similarity in conformation between the two, shown by the locations of corresponding atoms at the five places marked a, b, c, d, e.

mone (LH-RH) at X_2 and X_3 in its natural sequence Tyr_1-Gly_2-Leu_3-Arg_4-was first shown to be stabilized and made more active by the introduction of a **D**-side chain at the Gly α-carbon atom. This agrees with ideas on the so-called Type II β-turns, which is explained below. However, the same workers found that the activity of LH-RH is equally well improved by producing a γ-lactam ring using the **L**-configuration at the Gly carbon atom for this purpose. The interesting point is, once again, that the β-carbon atom corresponds to the **L**-configuration at C^α for the γ-lactam ring, while it corresponds to the **D**-configuration for the linear peptide which showed increased activity. Once again we see the "**L** imitates **D**." This can be generalized, and it can equally well happen that **D** can imitate **L** under suitable circumstances in other compounds, especially those having the conformation of a **L-L** β-turn (which is very common).

This may look very strange to you, but actually, it is easy to understand, when we realize that the (ϕ, ψ)-map throws away a large range of combinations of ϕ and ψ the moment there is a side chain that is free. This is because of a van der Waals contact larger than 3Å that is required between non-bonded atoms. But if the same β-carbon atom is covalently linked to the nitrogen, either directly as in the β-lactam ring, or through an intermediate atom as in the γ-lactam ring, then the distance between C^β and N is less that 2Å. Such an **L** type C^α–C^β bond occupies the place forbidden for the **D**-type C^β in a *free side chain*, and by the C^α–H^α bond in that case.

This idea has immense possibilities for the synthetic drug chemist.

The Beta Burn. This brings me to a brief discussion of the β-turns–a conformational feature of protein and peptide chains. We are proud of the fact that this β-turn, which has now become one of the most important subjects of study in protein biochemistry as related to conformation, was actually enunciated and proposed from our laboratory in Madras. It was given in the Ph.D. thesis of C. M. Venkatachalam and I had the great pleasure of seeing the report on this thesis written by Prof. Scheraga. You may all be surprised by the fact that the Universities in India never allow a Professor to see the reports written by the so-called examiners on the theses of their students. In this particular case, Prof. Scheraga had the kind courtesy to send me a copy of the report which he had sent to the University, and I was really thrilled to read in it a statement to the effect that, in his opinion, Venkatachalam's thesis came up to the highest standards of any Ph.D. thesis in his field in U.S.A. (Figure 7).

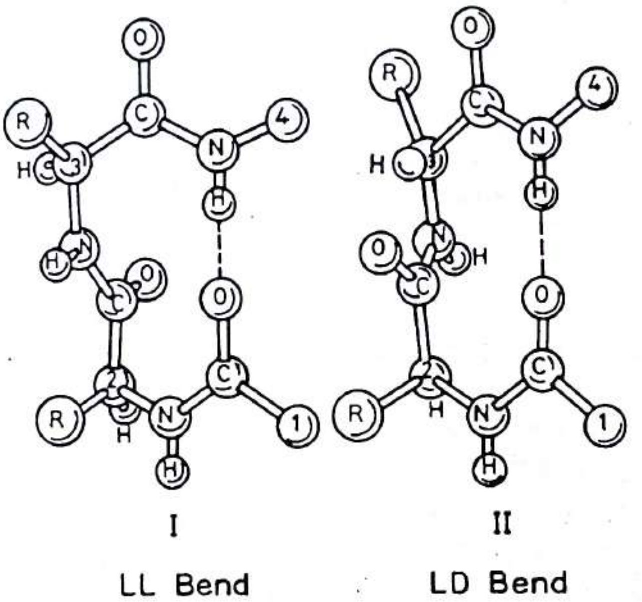

Figure 7: Perspective diagrams of the two standard types of beta-turns. See also Table II.

When the β-turn was proposed from our laboratory (20) (which incidentally is of two main categories–Type I and Type II–both of which were pointed out by Venkatachalam and a Type III closely similar to Type I, but which forms part of the 3_{20}-helix), it was realized that one of them (Type II) will not incorporate an **L**-amino acid in the third location of the sequence -R_1-R_2-R_3-R_4-, but only glycine can occur there, normally. We had not realized at that time that **D**-amino acids occurred fairly commonly in antibiotics, although they occur very rarely in normal compounds taking part in biological metabolism. Therefore a couple of years later, Chandrasekaran and I worked on this so-called **L-L** and **L-D** turns (standing for β-turns of Type I and II) in Chicago. This (21) pointed out the great stability that the **D**-amino acid imposes, in replacing Gly in Type II turns. The reason is very simple, namely that the **D** side group lends additional stabilizing energy in the region R_3, (but an **L** $C\beta$-atom destabilized it). This again is a fact, which the pater I mentioned above on LH-RH had demonstrated so beautifully (Table II).

Side Chains of Amino Acids. Since the side chain has played such an important part in the conformation of the backbone itself in peptide and protein chains, a very systematic study of all types of amino-acid side chain was taken up by Sasisekharan and a number of his colleagues, notably Lakshminarayanan and Ponnuswamy. Theses studies were started in the late 1960's (22) and almost all the 20 amino acids were studied. It was a great pleasure at the early stage of the subject for us to see which amino acid will have which side-chain conformation, and it

Table II

Conformational Angles Phi and Psi for the Common Beta Turns[1]

Type[1]	Nature of R_2,R_3	(ϕ_2, ψ_3)	(ϕ_3, ψ_3)
I	**L,D**	(-60°,-30°)	(-100°,10°)
II	**L,D**	(-60°,120°)	(80°,0°)
III	**L,L**	(-50°,-30°)	(-50°,-30°)
I′	**D,D**	(60°,30°)	(100°,-10°)
II′	**D,L**	(60°,-120°)	(-80°,0°)
III′	**D,D**	(50°,30°)	(50°,30°)

[1] The hydrogen bond is 4 → 1 for all of them.

[2] I′, II′, III′ are mirror images of I, II, III and therefore, **L** and **D** are interchanged between the two.

was very reassuring when we found that not only were these confirmed by observation in small compounds, but even by the observed crystal structures of globular proteins. Nowadays, data of this type is of common knowledge, and it is even contained in the *Handbook of Biochemistry and Molecular Biology*.

Beginnings of Energy Calculations. One of the very essential features that specifies which of two possible conformations, both of which are equally likely, will be preferred is the occurrence of hydrogen bonds–particularly of the types NH...O and OH...O. Therefore, in trying to calculate the energies, it is necessary to have a potential function for these. (I am not mentioning much about the early development of the energy calculations since our laboratory played only a secondary part in that feature.) The first energy approaches to protein structures were given in 1956, by Liqouri (25), Flory (24) and Scheraga (25) almost simultaneously. We got into it almost immediately and preferred the Flory formulation of the potential functions which can be considered to be one belonging to scientific philosophy, namely, the application of statistics and probability to energies, and therefore I shall discuss it in some detail.

Statistical Methods for Conformational Analysis

Probability and Energy of Hydrogen Bonds. Although this approach is widely used nowadays in several in several aspects–for example, for the prediction of secondary structure from sequence, as has been done by Gerry Fasman and Chou (26), –it has not been sufficiently realized that earlier attempts at applying statistical methods for such purposes were made in our laboratory. In the early 1960's along with Dr. C. Ramakrishnan who was the co-author of the first paper (ϕ, ψ)-map, I investigated in great detail the distribution of the length /(NH) and the angle θ = NH A NO in NH...O hydrogen bonds. It was a very laborious work and we took almost all available data at that time and this was published in the Proceedings of a Symposium on Fibrous Proteins which took place in Canberra in Australia. Soon thereafter, we wanted to make use of this in predicting the energy distribution as a function $E(l,\theta)$ of l and θ from the probability distribution $p(l,\theta)$. (27) For doing this, we used the Boltzman distribution:

$$p(l,\theta)\ \alpha\ e^{-E(l,\theta)/RT} \qquad [1]$$

This formula met with severe opposition because the Boltzman distribution had been proved and is utilized in physics only for energy distribution among molecules, or components of molecules which are in statistical equilibria. I had a long discussion with Professor Pauling about this when he came to Bangalore and I pointed out to him that the energy values so determined fitted beautifully into predictions of structures for biopolymers and similar compounds. He was noncommittal and said in effect; "If you find that it is empirically satisfactory, go ahead and use it" I have still not got the complete theory to support this distribution, although I have some vague ideas which I will not present here. The essence behind this is simply the fact that a conformation, which is expected to be rarely observed because of the higher energy involved, will in fact be rarely observed. The second "rarely observed" in the above sentence refers to $p(l,\theta)$ of Eq. (1) while the first "rarely observed" refers to the calculated energy $E(l,\theta)$ of it. Any relation of the type of Eq. (1) will fit this; the only point at issue is whether the constant used should be RT or some other number.

In fact, this is a dictum of probability theory–namely that if a certain probability distribution is observed connecting one property with another property *of a population*, then the joint probability distribution can be equally well applied for predicting the second from the first, or the first from the second, *in particular cases*. Hence, it is obvious that *the statistical method of approach can predict conformations only in a statistical way*, and one should not be surprised if it gives completely wrong results in a particular case. If enough examples are tried, the fit will surely be good.

Rarity of cis *Peptide Units*. This statistical approach for obtaining the energy distribution function has been used in our laboratory in a number of ways. For instance, we know that the classical definition of the "partition function" in statistical mechanics which connects free energy with probability employs RT as the exponential parameter connecting the two. We used it, in particular, to explain the relatively rare occurrence of *cis* peptide units in relation to *trans* peptide units in protein and polypeptide chains, by using Eq. (1) in reverse. Although the difference in energy between these two states of a single peptide unit is only of the order of 2 to 3 kcal/mole the observation is that *cis* peptide units are extremely rare and are almost never found except for proline and for N-methylamino acids. A very elegant explanation of this was given by us in terms of the partition function obtained from the distribution of states in the $(\phi,\ \psi)$-maps of a stretch of three peptide units. (28) The calculations showed that, for the common amino acids with a C_β-atom, the probability of a *cis* conformation in the middle peptide unit was extremely rare in relation to its having a *trans* conformation. However, for proline, the two were found to be practically of the same probability. This beautiful result has resolved what I had considered earlier to be one of the unsolved problems in peptide and polypeptide conformations. However, it does not mean that a *cis* peptide unit can never occur for residues other than proline; it can do so under special circumstances when the conformation of the chain and its local environment produces restrictions, requiring such a unit to be present. In other words, there is no mystery about *cis* peptide units being rarely observed, except that it is a highly unlikely conformation for a three-peptide chain unconstrained by other considerations.

We also employed this statistical approach to determine the nature of the ϕ- and ψ-potential functions for amide units as they occur in a peptide chain, by actually looking at the distribution in the $(\phi,\ \psi)$-map of various local conformations at the C^α-atom, and comparing it with the contribution expected from the intermolecular van der Waals and repulsive interactions. It is rather surprising that the potential functions so obtained showed fairly steep maxima and minima for ψ with a barrier of more than 2 kcal/mole, as against a small value of less than 0.5 kcal/mole that had existed in the literature. It was also verified from carefully devised quantum chemical calculations that this type of variation is to be expected.

Application of Quantum Chemistry to Peptide Conformation

This is the right opportunity to talk briefly about quantum chemistry and how it can help in conformational analysis. The above analysis of the ψ-potential and the associated quantum chemistry was done by my colleague Kolaskar with others in the department. Earlier, he was associated with Lakshminarayanan and me in studying the non-planarity of the peptide unit–a feature which we had pointed out to be of importance to biomolecular structure even in the 1968 review (30) in *Advances in Protein Chemistry*. Since then, several persons, including Dunitz in particular, had analyzed crystal structures from this point of view and showed that non-planarity was not at all uncommon. However, no definite indication was available from theory as to how much of non-planarity is to be expected and what is the energy associated with it.

Catalysis of the Theory of Non-planarity. Our entering this field was catalyzed by a remark made by Prof. Mullikan commenting on my lecture that I gave on peptide conformation in Chicago. I greatly emphasized the importance of the planar peptide unit, and its dimensions as determined by Pauling, for the stereochemistry of peptides, and how it had helped in working out so many problems in peptide and protein conformations. Mullikan asked me, in particular, whether I believed that non-planarity cannot at all occur, and he suggested that the very fact that ammonia is pyramidal indicated that, even in the peptide unit having a partial double bond character for the C–N bond, the three bonds meeting at the nitrogen atom need not be completely planar. The very next week, Lakshminarayanan and I started making quantum chemical calculations to test this idea, because there was no other approach to it that could give a definitive answer. Using CNDO calculations, we showed that large non-planarity ($\Delta\omega$), of about 10°, can occur about the C–N bond, and the rotation angle ($\Delta\theta_N$) between the N–Ca and N–H can also differ from 180° by double this order of magnitude. Immediately, our attention was brought to a microwave study made in Japan several years earlier on formamide (H–CO–NH_2), in which a non-planarity of this order had been observed at N. It greatly strengthened our confidence in the result from quantum theory. However, when we applied INDO for this purpose, the predicted deviation was rather smaller, though still appreciable, and deviations from the planar structure of up to 10-15° of non-planarity, at the N atom, did not involve increased energies of more that 0.5 kcal/mole. On the other hand, both CNDO and INDO indicated very little non-planarity of the three bonds meeting at carbonyl carbon atom. (31)

For a few years thereafter, Kolaskar spent considerable time in checking various available data and confirming, by the probability method mentioned above, not only that the distribution on non-planarity is what is given by theory, but also that the order of magnitude of energies involved was also in agreement with observation, if Eq. (1) is taken to be valid (see Figure 8).

Non-planarity and its Consequences for Peptide Conformation

This is the right occasion to talk of the application of the non-planar peptide unit in polypeptide structures. In the beginning, we found several examples in simple peptides and cyclic peptides, with appreciable non-planarity, as calculated by using accurate data from crystal structures, in which there was no reason why the packing in the crystal should have lent a hand for the production of non-planarity. A slight non-planarity was found for the α-helix on energy minimization, which agreed that what Arnott had found by a refinement from x-ray diffraction

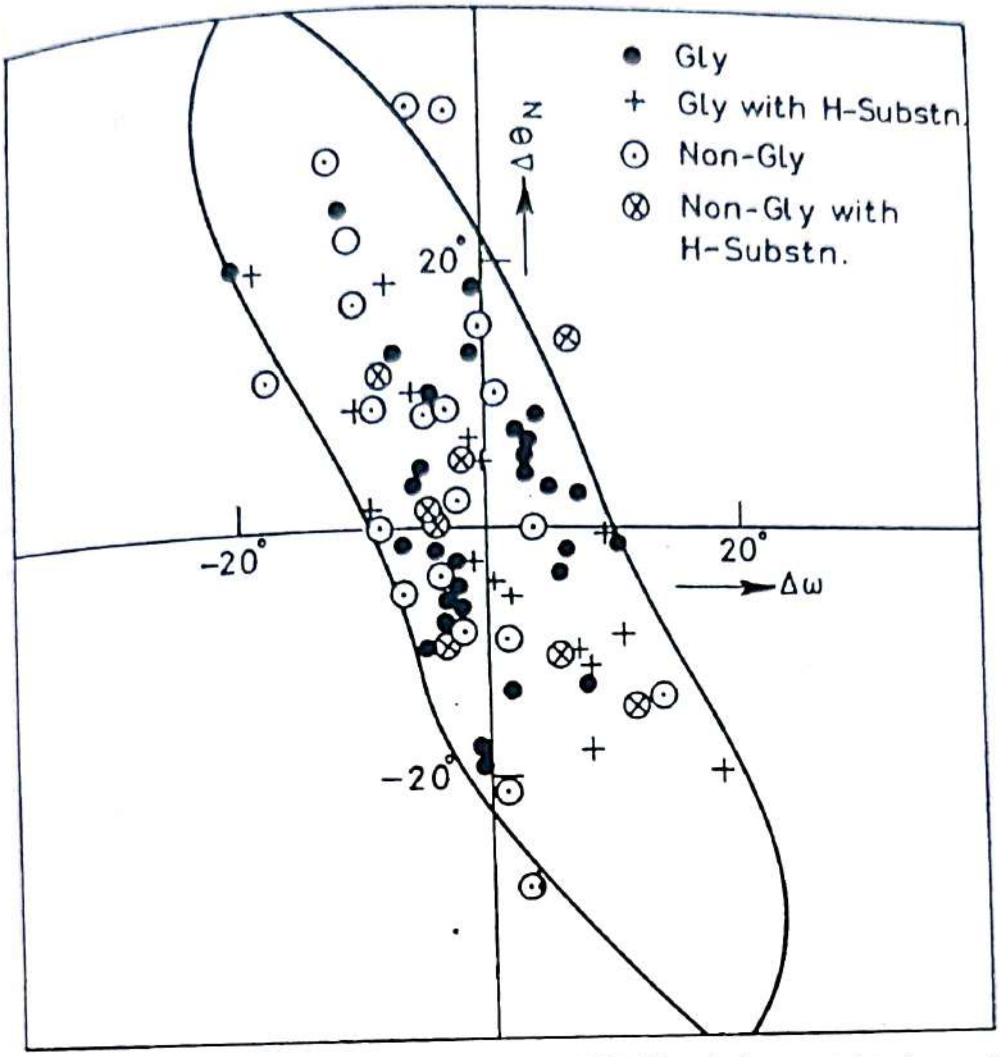

Figure 8: Energy map obtained from quantum chemistry (INDO) and observed data in good crystal structures of peptides. (Symbols explained in text.)

data; but it was nothing to talk about. The general conclusion, of value to those who build protein structure, was that one need not worry about including non-planar units with up to 20° non-planarity ($\Delta\theta_N$) at the nitrogen atom, and a range of about ±10° for the dihedral angle $\Delta\omega$ about the standard value of 180° for a *trans* peptide unit.

Left-handed δ-helix with Non-planarity. There the situation stayed until, by a curious coincidence, my attention was drawn to a possible left-handed helix of the α-type for a polypeptide chain. This was brought to my attention, at the NMR conference in Stanford, by Jardetsky, as a probable conclusion of some of his NMR data. A brief inspection of the model he showed me indicated that this helix was of a topology different from the α-type helices. Although the ω-helix is left-handed, it has only $j \rightarrow 1$ hydrogen bonds, while in the helix built by Jardetsky it was $1 \rightarrow j$.

I told Jardetsky that we should be able to find, by calculation, the best helix having this topology. But, I also remarked that, only a year earlier, Ramakrishnan in our laboratory had made a thorough search of every possible type of single helix that could occur for peptides, and had shown that all the possible ones had been listed and no new ones would be found if the currently accepted ideas of energy of stabilization were used. This was the dilemma; but then it occurred to me that the solution might lie in *non-planarity*. I was at the N.I.H. at that time and had no assistants, and therefore I telephoned Chandrasekharan, who was at Purdue, and told him to find the minimum energy conformation in the region having this particular helicity, including also non-planarity. Surprisingly, Chandrasekaran then found a good minimum in the expected region of Jardetsky's left-handed helix, for poly-L-alanine. Although it was not as stable as the right-handed α-helix, it was probably superior to all the left-handed helices of the type that were considered to be possible, like α_L and ω.

Therefore, I examined other polypeptides as likely candidates for this new left-handed helix with about –4.0 residues per turn. Earlier, in Madras, we had found that poly-L-serine could form an OH...O hydrogen bond between the side chain -$C\beta H_2$-OH and the backbone O=C, if it had a *left-handed helical twist* of the usual α-type. On checking the same polypeptide for the new left-handed helix, I found that a similar hydrogen bond could exist for this also. I this were true, then this would also be true for the side chain -$C\beta H_2$-NH_2. The corresponding polypeptide is poly-PDPA (standing for poly=**L**-diamino-propionic acid). This is an analogue of lysine and ornithine, with one less CH_2 group than ornithine. On checking with models, I found that both lysine and ornithine were not specially suited for the new helix, but the side chain of PDPA was very good for forming a hydrogen bond with the backbone.

I left it at that; but imagine my surprise, when in 1978, at the annual Biophysical Society Conference in Washington, J. T. Yang of San Francisco, to whom I talked about this, told me that he had already discovered that **L**-PDPA had a left-handed helix, while both poly-**L**-lysine and poly-**L**-ornithine assumed only the right-handed helix, while both poly-**L**-lysine and poly-**L**-ornithine assumed only the right-handed helical configuration, as detected by ORD-CD studies. I was then absolutely convinced that our ideas about the new left-handed helix were right, and we decided to name this as the δ-helix. A paper was published on the theoretical study, and possible interpretations of NMR and ORD-CD data employing this helix, by Chandrasekaran and Jardetsky (8).

We can now show that the δ-helix is the stablest of all left-handed polypeptide helices. In fact, my former colleague Manju Bansal, told me two weeks before preparing this lecture, that she had definitely established that the helix which occurs for poly-β-benzyl-L-aspartate (PBLA) is the new δ-helix having $n = 4.0$ and not the ω-helix which is usually supposed to occur (9). The proof from theory was obtained by taking into account especially the potential energy associated with non-planarity of the peptide units, and also the various improvements in the potential functions which I mentioned above, including, in particular, the idea of softening the contacts H...H and C...H which I had suggested in my contribution to the Jerusalem symposium in 1975 (29). We can now exclude the ω-helix from the list of possible helices since its minimum energy for PBLA is about 10 kcal/mole above that of the δ-helix. (So it has not been listed in Table I). All examples where the former had been postulated should be checked for fit with the new δ-structure.

Need for Looking Out for Unexamined Possibilities

The above is a very good example where, an entirely new possibility could be found out, although a thorough re-examination of the available data and theory indicated that no new polypeptide helix was expected to occur at all. Thus, from the point of view of scientific philosophy, one must have one's eyes and ears open for new type of knowledge leading to new possibilities, even though they are completely at variance from accepted theory. As the famous Indian poet Kalidasa mentions:

Purāṇamityeva na sādhu sarvaṁ
Na cāpi kāvyam navamityavidyaṁ.

(Not all that is old is necessarily true;
Nor a poem be unread, because it is new.)

This shows that this problem has been there all along in human existence, and will continue to exist. The bright young man has always to fight the established order, before his new ideas are accepted.

The Nucleic Acid Dilemma. I shall therefore briefly consider what has happened similarly in the case of the DNA double helix. The postulation of the double helix in 1952 by Watson and Crick from stereochemical and base-pairing principles was proved by the work done in King's college in the succeeding years. The x-ray patterns of many polynucleotides agree with that of the DNA double helix. Apart from the existence of minor modifications such as A-DNA and B-DNA which had different number of units per turn, both of which had essentially the same *right-handed* twist of about 30-40° and base pairing of the Watson-Crick type, only minor examples had been found where slightly different configurations existed. However, whenever I talked to biologists during the late 60's and early 70's, when so many experimental studies had been made on DNA as it occurs in the nucleus of the cell, they always had a difficulty in reconciling the way in which a nucleic acid chain will have to untwist itself some millions of times in one molecule of DNA and then, after duplication, retwist itself in the same way without any tangling taking place, with the absolute reproducibility of genetic information achieved by the process. I was also worried very much about this feature, and frequently talked about this to experts in DNA conformational theory–particularly with Sasisekharan of our laboratory. Independently, Sasisekharan had himself thought about the possible existence of left-handed helices for DNA and had stereochemical calculation showing that it had a very reasonable structure and could possibly occur. However, this matter was under eternal discussion between biochemists, microbiologists, molecular biologists, and molecular biophysicists, and no clear solution to the tangling problem was available.

During 1975-76 I took a serious interest in this, and thought that the matter could be resolved by putting the two chains of DNA side by side, but having some sort of wavy structure so the the helical x-ray pattern would be simulated. In fact, I even went to the extent of making some drawings of the chain that would have the same repeat as normal DNA, and calculated the expected diffraction pattern using one lumped atom at phosphorus, another at the sugar, and the third at the base. The model was extremely crude and was of the 1950 era. But the interesting thing was that the calculated Fourier transforms were compatible with the observed pattern, as judged by discrimination between regions of large intensity and those of small intensity. All these only showed that the net radius, or the net width, of the structure was correct and the two chains had some sort of helicity with the same pattern as in DNA.

However, the whole approach had to be thrown away because Sasisekharan showed unmistakably that such an arrangement cannot be realized in an actual DNA structure. He was sure that, if we assume that the two chains do not twist around one another, but only stay side by side, then no such structure can be built which is free of bad contacts. In fact, I would consider this a very great achievement for a nucleic acid expert, because I myself was completely baffled by the number of dihedral angle that are there in DNA, and the number of inter-connections that had to be considered. To say with confidence that something is not possible required a very great feeling for the molecular structure.

The New Structures for DNA. Taking his clue from these discussions in the department, which raised the question whether the intertwisting of the two chains in DNA is a biological possibility (quite apart from the chemical possibility on the specimens which give the beautiful diffraction patterns recorded for crystallized B-DNA), Sasisekharan then tried to fit a structure, in which, the structure is right-handed for about 5 units, and is then left-handed for about 5 units, so that there is a repeat after about 10 units as is found in B-DNA. Here again, an enormous amount of intuition and knowledge of how these structures would look like was necessary in order to show that something is possible from stereochemistry. When I tell you that, even if some of the dihedral angles and bond angles were changed by 1/2°, the net unit twist would go away by a magnitude of the order of 29°, one can realize the complexity of the problem. Yet, Sasisekharan showed that such a structure is quite satisfactory, and much of it was made possible because he already had the coordinates for the left-handed DNA helix. He published this work first in *Current Sciences* (33). This work of Sasisekharan clearly showed that the principles of stereochemistry will allow the double helix to assume both the right and left handed spatial configurations and that both types of structures may coexist in the double helix.

As you all know, the matter stood at that, and it took some time before some of these structures were actually realized in examples where they could be unmistakably shown to occur. Thus a short stretch of non-right-handed helix was observed in oligo-nucleotides by Viswamitra in 1978 (34), and the left-handed helical twist by Rich in 1979 (35) and by Dickerson in 1980 (36). Recently Wells and coworkers (47) have managed to construct a recombinant plasmid DNA in which right and left handed helices. It has been demonstrated by Sarma and coworkers (48) that under solution conditions poly(dG-dC)·poly(dG-dC) in high salt exists as a left-handed Z-helix.

I will not say more about this, mainly because I am not a specialist on poly-nucleotides and the above comments of mine have been made only as a biopolymer chemist viewing the subject as a whole. A recent review by Sasisekharan (37) contains references to the relevant literature. (49)

Suggestions for Future Studies

I shall now give a brief account of some ideas that I have regarding types of problems in biochemistry and molecular biology, which could be attacked profitably from the point of view of conformation. They are, by no means, exhaustive.

Molecular Fit. The concept of "molecular fit" occurs, for example, in the binding of the substrate to an enzyme. A very similar problem is that of antigen-antibody recognition. As Pauling

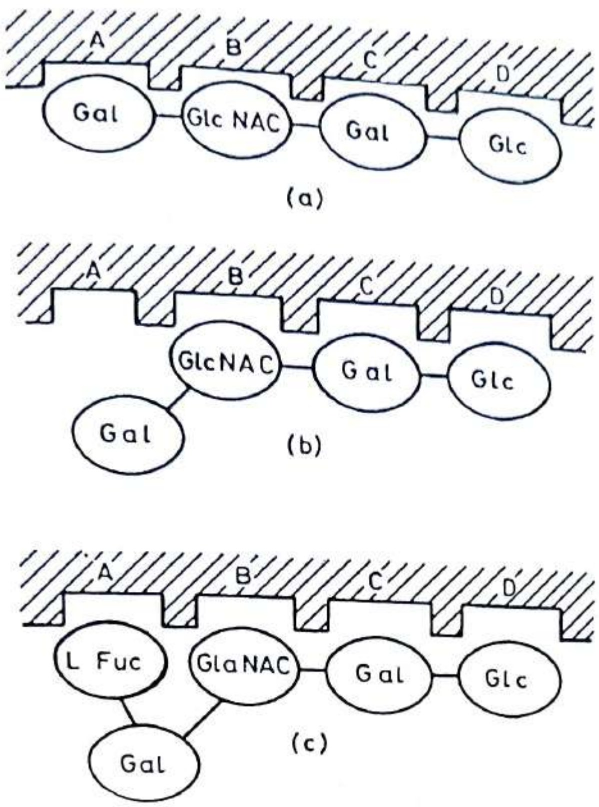

Figure 9: Schematic representation of compounds (a), (b) and (c) (see text), in relation to the binding pockets in the receptor. Note how the Gal in (b) is pointed away from the binding site, with the additional L-Fuc in (c) restores the situation as in (a).

and Delbrück (38) pointed out as early as 1940, the essence of the phenomenon is the pairing of a specific arrangement of atoms in one molecule with that in the other molecule which comes and attaches itself to it.

Recognition by Antibodies. That this is not too difficult, and that some apparently contradictory facts can be given a sound explanation from a proper understanding of conformational theory, has been shown in Bangalore by Rao and co-workers (40). It is commonly supposed that, in the saccharide chain of an antibody, it is the terminal sugar residue that gives much of its specificity. However, in the case of two such compounds, lacto-N-neotetraose (*a*) and lacto-N-tetraose (*b*), both of which have the same end group, galactose the former has the specificity for binding, while the latter does not bind at all. The only difference between the two is that the former has an 1 → 4 linkage of galactose to N-acetyl-glucosamine, while it is 1 → 3 in the latter between the same two sugars. However, if one adds an L-fucose residue to the second compound with a 1 → 2 linkage to obtain lacto-N-fucopentaose then a good amount of the binding is restored. These are known facts, which look puzzling. However, considering that not only the terminal residue, but two or three others next to it in the chain, are also responsible for recognition and binding, Rao showed that if the proper energy-minimized conformation of the above three compounds are compared, *then the shape, as far as binding is concerned, is very similar as between (a) and (c), but different in the case of (b)*. This is shown in Figure 9, and this is an example where a carfu study of the relevant saccharide conformation helps in understanding the apparently strange behavior that is observed.

Protein-Nucleic Acid Interactions. This is a subject in which there are more expert specialists than I taking part in this conference, and so I shall only touch upon it. The importance of intercalation within the nucleic acid chain, preventing its normal structure from being expressed, is

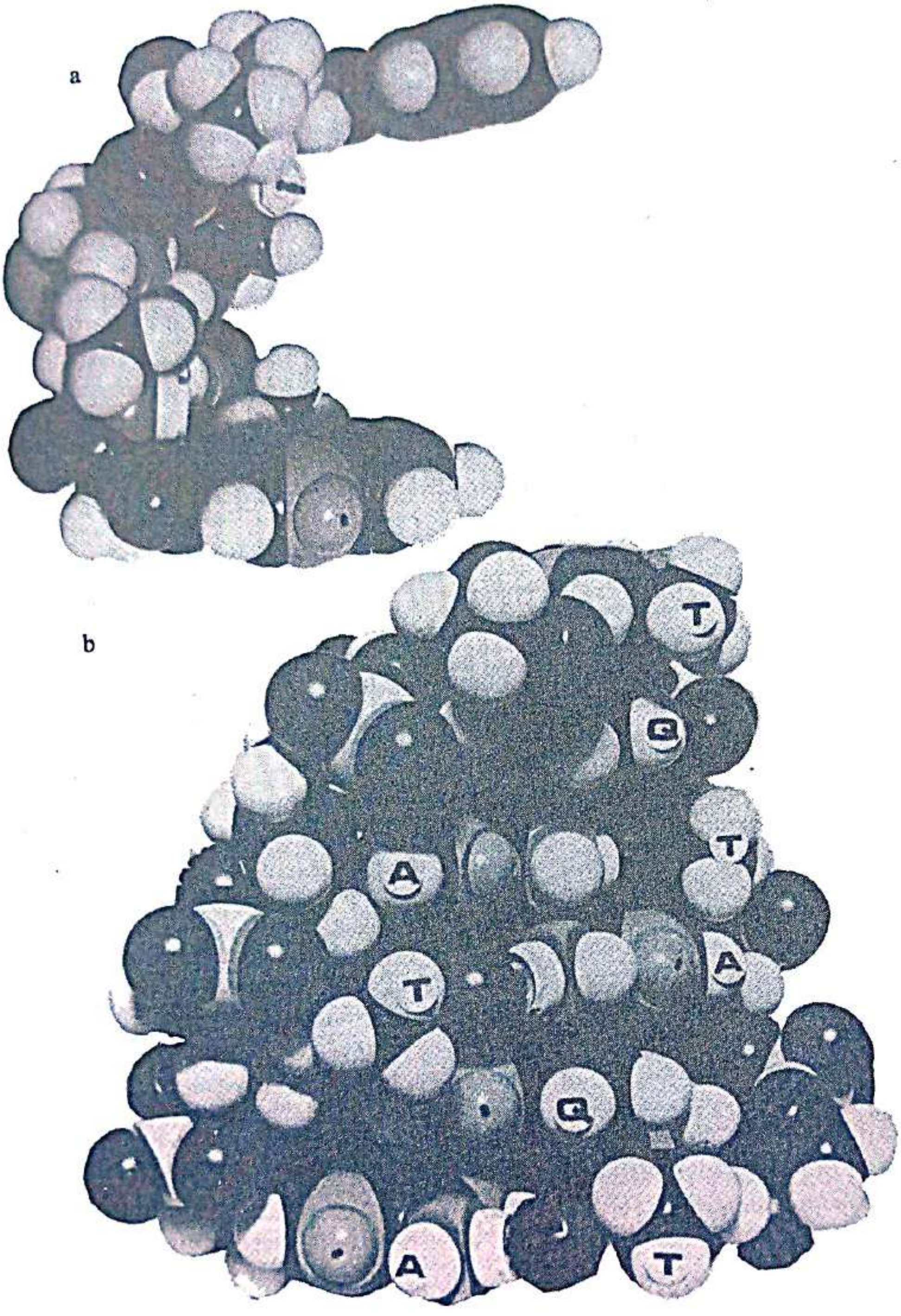

Figure 10: (*a*) CPK model of TANDEM molecule, slightly modifies from the x-ray structure. (*b*) CPK model of TANDEM in its complex with a partially unwound B-DNA helix, seen from the major groove side.

well recognized, particularly in relation to certain types of antibiotics and carcinogenic compound. However, precise knowledge as to haw a peptide unit, or its side chain, fits into a nucleic acid chain is not yet available, nor even the principles connected with the stereochemistry of it. In this connection, I would like to draw your attention to a recent paper by Viswamitra (41) on the x-ray crystallographic study of the synthetic analog, TANDEM, of the antibiotic drug triostin A, using the data of which, the first detailed picture of the association of a cyclic peptide with the DNA chain having a specific sequence has been worked out–see Figure 10.

Stereodynamics. Finally, I come to the topic which is particularly emphasized in the Conversation–namely the stereodynamics of molecules. Dynamics is more difficult to work out than statics. However, efforts by Karplus and others in this direction have been very rewarding. I may point out two particular aspects where the dynamic action has to be studied in particular. One could be the way in which the active site of an enzyme moves over the surface, or the chain, of a biopolymer (like a protein) and reaches the particular specific sequence where the cleavage, or some other reaction, takes place. There is reason to believe that the recognition is there, not only of the actual substrate region where the reaction takes place, but also of the amino acids on either side up to 3 or 4 residues away. The dynamics of the "crawling" motion has to be understood, in addition to the phenomenon of "matching."

Similarly, the problem of ion transport across membranes, and its modifications by ion transport peptides, is a very important problem to be examined. Thus, molecules like gramicidin-A, have a special type of helix–the so-called **LD** helix–first worked out by Chandrasekaran and myself (42,43), although I have not touched upon this in this review. This helix has a central hole through which the ions are transported. However, the ion has to be of the right size–neither too small nor too large. If it is too large, obviously it cannot be transported through the hole, while if it is too small, it just goes in and comes out. When it is of the right size, one section of the tube takes hold of the ion, and moves it on to the next section, apparently in some sort of peristaltic process. The dynamics of this, and the way whereby the amount of transport, normally taking place across the membrane, is enormously magnified by the peptide, should be examined. This will have the reward that it might be possible to design newer and better antibiotics of the gramicidin-A type.

Need for Elementary Book on Conformation. This brings me to the last topic, namely the need for more elementary books on conformation specially intended for the biochemists and the biologists, who would like to employ for their studies, the methods of reasoning adopted by physical chemists and chemical physicists. Since it is a way of thinking that has to be passed on to the biochemist and the biologist, and not merely a technique, there is a great need for books written on conformation where the emphasis is on the role of conformation related to biomolecules and biological activity, rather than on the principles of calculating energies and physicochemical factors. Even the beautiful book by Dickerson and Geis (46) has to be supplemented by another which will also explain the theoretical approach to the subject, in addition to the "what" and "how" of it that has been beautifully pictured and explained therein.

As in every science, conformational analysis has started as a specialty, and developed as a specialty; but I think it has now come to a stage when it can be made available to one and all.

Acknowledgements

Most of the material in this review was dictated from memory, and I beg to be excused for minor inaccuracies in the text, although I hope there are no serious errors. I wish to thank M. Suresh, M. V. Manjula and R. Manjunath, for typing several drafts of this report in less than three weeks, and for helping in the preparation of figures, tables, etc. This work was done during the tenure of a research grant on "Application of Epistemilogy to Mathematics, Physics and Biology," provided by the University Grants Commission, India.

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G. N. Ramachandran, GNR to those who know him well, is one of the most brilliant Indian scientists of this century. He has been rightly called "the father of molecular biophysics in India". He was a pioneer in that field even when the subject was just commencing to take shape in the advanced countries of the Western world. Gifted with uncontainable brilliance and intelligence, driven by inexhaustible energy, against impossible odds – primitive equipment, gargantuan Indian bureaucracy, dilapidated communications, deliberate delay tactics by Western journals, caste discrimination – he triumphed, and immortalized himself in the field of molecular biophysics and protein conformation.

This book is the story of a gift from the gods to India, a young tamil brahmin from the Malabar coast, his triumphs, ecstasies, agonies and defeats; and how India lost its chance to become the power center in structural biology.

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